

CONTENTS OF VOLUME 38

DECEMBER, 1926 NUMBER 6

	PAGE
Analysis of Heart Sounds H B Williams, M D, and H F Dodge, S B, A M, New York	685
The Mechanism of Pain in Gastric and in Duodenal Ulcer II The Production of Pain by Means of Chemical Irritants Walter Lincoln Palmer, M D, Chicago	694
Chronic Biliary Tract Disease The Diagnostic Criteria John G Mateer, M D, and W Stuart Henderson, M B, Detroit	708
The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels William F Petersen, M D, and George Milles, S B, Chicago	730
Hyperthyroidism, Myxedema and Diabetes Russell M Wilder, M D, Rochester, Minn	736
Cardiac Capacity Determined by Standardized Effort Preliminary Report Joseph B Wolffe, M D, Philadelphia	761
The Basal Metabolism in Beriberi Seizaburo Okada and Euchi Sakurai, Tokyo, Japan	770
The Use of Insulin by Mouth H R Miller, M D, New York	779
The Growth of the Long Bones in Childhood, with Special Reference to Certain Bony Striations of the Metaphysis and to the Rôle of the Vitamins H A Harris, M B, St Louis	785
Primary Carcinoma of the Thymus Report of a Case I I Lemann, M D, and John Smith, M D, New Orleans	807
The Spectrophotometric Analysis of the Color of the Skin, and the Observa- tions by This Method in Normal and in Pathologic Subjects Charles Sheard, Ph D, and George E Brown, M D, Rochester, Minn	816
Book Reviews	832

INSENSIBLE PERSPIRATION ITS RELATION TO HUMAN PHYSIOLOGY AND PATHOLOGY^{*}

FRANCIS G BENEDICT, PH D

AND

HOWARD F ROOT, M D

BOSTON

The changes that occur in the body weight from day to day or, indeed, from hour to hour are unnoticed by most persons, probably because the body weight is fairly constant for weeks at a time. Large losses in weight, such as those which result from extreme exercise and profuse perspiration, as in athletic contests, are easily recognized, but smaller losses or increases are not so apparent. Thus, during the day variations in body weight amounting to several pounds, directly attributable to the ingestion of food and drink and the passage of feces and urine, may not be noted because it is not the custom to record the body weight frequently throughout the day and often the appliance on which the body is weighed is not accurate enough to show changes in weight of less than 1 pound or 0.5 Kg. Such alterations in body weight are easily understood, however, because they are visible changes. But the weight of the food and drink is not entirely compensated by the weight of visible excreta. There is also an invisible loss of gaseous substance in the form of carbon dioxide and water vapor, given off both from the lungs and the skin. This invisible loss may sometimes amount to 70 Gm. in an hour, even though the subject is quiet and resting. The share that these invisible, gaseous losses play in the twenty-four hour loss in weight is today but imperfectly appreciated, although it was considered of great physiologic importance three or more centuries ago.

Sweat can be seen and this visible perspiration can readily be perceived to represent a loss of material from the body. The invisible loss is not so readily recognized and a delicate balance must be relied on to establish it. The appearance on a cold, frosty morning of condensed

^{*} From the Nutrition Laboratory of the Carnegie Institution of Washington and the New England Deaconess Hospital, Boston.

^{*} This paper is no. 63 of a series of studies in metabolism from the Harvard Medical School and allied hospitals, the expenses of which have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSSEPH I MILLER, Chicago

RICHARD C CABOT, Boston

WARFIELD T LONGCOPE, Baltimore

GEORGE DOCK, Pasadena, Calif

WALTER W PALMER, New York City

W S THAYER, Baltimore

VOLUME 38

1926

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO

CONTENTS OF VOLUME 38

JULY, 1926 NUMBER 1

	PAGE
Insensible Perspiration Its Relation to Human Physiology and Pathology Francis G Benedict, Ph D, and Howard F Root, M D, Boston	1
The Rate of Urea Excretion as a Test of Renal Function by Means of a Modification of McLean's Index Shohei Kawahara, M D, Rochester, Minn	36
Gastric and Duodenal Ulcer Frequency, Number, Size, Shape, Location, Color, Sex and Age in Seven Thousand Seven Hundred Necropsy Records at Bellevue Hospital, New York Mills Sturtevant, M D, and Louis L Shapiro, M D, New York	41
Edema I Correlation of Elastometer Findings, Disappearance Time for Intradermally Injected Salt Solution, Urinalysis and Nitrogen Retention of the Blood in Edema Margarete Meta Kunde, Ph D, Chicago	57
Stenosis of the Isthmus (Coarctation) of the Aorta and Its Diagnosis During Life Report of Four Cases John T King, Jr, M D, Baltimore	69
The Rôle of Insulin in Protein Metabolism N W Janney, M D, and I Shapiro, M D, Los Angeles	96
The Relative Importance of the Systolic and the Diastolic Blood Pressure in Maintaining the Coronary Circulation Fred M Smith, M D, G H Miller, M D, and V C Graber, M D, Iowa City	109
Auricular Fibrillation with Regular Ventricular Rhythm and Rate Over Sixty Robert L Levy, M D, New York	116
External Factors Causing Variable Results in the Kottmann Reaction Jacob Kasanin, M D, and Emily Knapp, A B, Boston	129
Water Metabolism IV Sugar Metabolism in Dehydration Edmund Andrews, M D, Chicago	136
Book Reviews	142

AUGUST, 1926 NUMBER 2

Clinical Physiology of the Stomach Simultaneous Quantitative Observa- tions on Gastric Secretory Volume, Acidity and Motility Arthur L Bloomfield, M D, and Chester S Keefer, M D, Baltimore	145
Hypertension and Constipation A Statistical Inquiry Walter C Alvarez, M D, R L McCalla, M D, and A Zimmermann, Dr es Sc, San Francisco	158
Diseases of the Liver V A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System Carl H Greene, M D, and H Milton Conner, M D, Rochester, Minn	167
Persistent Premature Contractions A Clinical Study Harold L Otto, M D, and Harry Gold, M D, New York	186

CONTENTS OF VOLUME 38

	PAGE
The Rationale of Therapeutic Puncture in Pericardial Effusions An Experimental Study Charles Spencer Williamson, M D, and Harold N Ets, M S Chicago	206
The Relation of Monilia to Infections of the Upper Air Passages A J Kotkis, M D, M Wachowiak, M D, and Moyer S Fleisher, M D, St Louis	217
Coronary Thrombosis with Congenital Absence of the Left Coronary Artery Fred M Smith, M D, and V C Graber, M D, Iowa City	222
Mycotic Aneurysms A Report of Two Cases Roscoe D Leas, M D, and Harvey S Thatcher, M D, Cleveland	226
Gastric Ulcer IV Experimental Production of Gastric Ulcer by Local Anaphylaxis Phillip F Shapiro, M S, and A C Ivy, Ph D, M D, Chicago	237
The Unitary Nature of Impairment of Renal Function Arthur M Fishberg M D, New York	259
Book Reviews	276

SEPTEMBER, 1926 NUMBER 3

The Occurrence of Benign Glycosuria in Diabetic Families J E Holst, M D, Copenhagen, Denmark	279
Pernicious Anemia, Achylia Gastrica and Combined Cord Degeneration and Their Relationship Roy R Grinker, M D, Chicago	292
The Effect of Atropine on Gastric Function in Man A Quantitative Study Chester S Keefer, M D, and Arthur L Bloomfield, M D, Baltimore	303
The Treatment of Polycythemia Vera (Erythremia) with Phenylhydrazine George E Brown, M D, and Herbert Z Giffin, M D, Rochester, Minn	321
The Pathogenesis of Lipoid Nephrosis Herman Elwyn, M D, New York	346
Epigastric Pulsation The Diagnosis of the Arrhythmia Cordis Through the Epigastriogram Nobutatsu Fukui, M D, Tokyo	360
Mycotic Aneurysm of the Aorta Fred M Smith, M D, and G H Hansmann, M D, Iowa City	367
The Pharmacology and Therapeutics of Novasurol A M Serby, M D, Chicago	374
The Basal Metabolic Rate in Cases of Chronic Cardiac Disease and in Cases of Hypertension Shepard Shapiro, M D, New York	385
The Use of Sodoku in the Treatment of General Paralysis A Preliminary Report H C Solomon, M D, A Berk, M D, M Theiler, M R C S, and C L Clay, M D, Boston	391
Acute Cocaine Poisoning and Its Treatment in the Monkey (Macacus Rhesus) A L Tatum, M D, and K H Collins, B S, Chicago	405
Book Reviews	410

OCTOBER, 1926 NUMBER 4

Glandular Fever (Infectious Mononucleosis) C W Baldrige, M D, F J Rohner, M D, and G H Hansmann, M D, Iowa City	413
Lipoid Nephrosis Francis D Murphy, M D, and Louis M Warfield, M D, Milwaukee	449

CONTENTS OF VOLUME 38

	PAGE
Carcinoma of Cortex of Suprarenal Gland with Virilism Report of a Case with Necropsy Henry M Feinblatt, M D, Brooklyn	469
Urea Retention A Simple Method for Its Estimation by the Mercury Combining Power of Blood Philip S Hench, M D, and Martha Aldrich, B A, Rochester, Minn	474
The Formation of Organic Acids and the Retention of Chlorides in Lobar Pneumonia Cai Holten, M D, Copenhagen, Denmark	489
Changes in the Chemical and Physical Characteristics of the Blood Following the Administration of Parathyroid Hormone, with Special Reference to the Clotting of the Blood A Cantarow, M D, W R Caven, M B (For), and Burgess Gordon, M D, Philadelphia	502
The Quantities of Serum Albumin Globulin and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies George Fahr, M D, and W W Swanson, M D, Minneapolis	510
The Combining Power of Proteins with Rose Bengal II Application as a Quantitative Test on the Spinal Fluid Sanford M Rosenthal, M D, and F Douglas Ackman, M D, Montreal, Canada	527
Peristalsis in a Loop of Small Intestine A Direct Study Laurence E Hines M D and H C A Mead, M D, Chicago	536
Aid in the Diagnosis of Typhoid Fever A New Laboratory Method C A Mills M D and K V Kitzmiller, M D, Cincinnati	544
Book Reviews	551

NOVEMBER, 1926 NUMBER 5

	PAGE
Chemical Changes in the Blood During Fasting in the Human Subject William G Lennox with the Assistance of Marie O'Connor and Margaret Bellinger Boston	553
The Output of the Heart per Beat in Hyperthyroidism I M Rabinowitch and Eleanor V Bazin, Montreal	566
Röntgen-Ray Therapy in Erysipelas E S Platon, M D, and Leo Rigler, M D Minneapolis	573
A Modification of the Urea Concentration Test Harold W Jones, M D, and Abram Cantarow, M D, Philadelphia	581
The Basal Metabolism of the Japanese Seizaburo Okada, M D, Enchi Sakurai, M D and Toshio Kameda, M D, Tokyo, Japan	590
The Mechanism of Pain in Gastric and Duodenal Ulcers I Achlorhydria Walter Lincoln Palmer, M D, Chicago	603
Renal Dwarfism Report of a Case Frederic W Lathrop, M D, Baltimore	612
Arachnidism Spider Poisoning Emil Bogen, M D, Los Angeles	623
Nontraumatic Left Diaphragmatic Hernia Clinical and Roentgenologic Studies in Fifteen Cases Henry K Pancoast, M D, and Russell S Boks, M D, Philadelphia	633
The Regulation of the Flow of Bile and Pancreatic Juice Into the Duodenum Glover H Copher, M D, and Shuichi Kodama, M D, St Louis	647
Direct Examination of the Gastric Juice A New Functional Test Arnold Galambos, M D, New York	654
Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister William F Petersen, M D, and David A Willis, M D, Chicago	663
Book Reviews	682

CONTENTS OF VOLUME 38

DECEMBER, 1926 NUMBER 6

	PAGE
Analysis of Heart Sounds H B Williams, M D, and H F Dodge, S B, A M, New York	685
The Mechanism of Pain in Gastric and in Duodenal Ulcer II The Production of Pain by Means of Chemical Irritants Walter Lincoln Palmer, M D, Chicago	694
Chronic Biliary Tract Disease The Diagnostic Criteria John G Mateer, M D, and W Stuart Henderson, M B, Detroit	708
The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels William F Petersen, M D, and George Milles, S B, Chicago	730
Hypert thyroidism, Myxedema and Diabetes Russell M Wilder, M D, Rochester, Minn	736
Cardiac Capacity Determined by Standardized Effort Preliminary Report Joseph B Wolfe, M D, Philadelphia	761
The Basal Metabolism in Beriberi Seizaburo Okada and Eiichi Sakurai, Tokyo, Japan	770
The Use of Insulin by Mouth H R Miller, M D, New York	779
The Growth of the Long Bones in Childhood, with Special Reference to Certain Bony Striations of the Metaphysis and to the Rôle of the Vitamins H A Harris, M B, St Louis	785
Primary Carcinoma of the Thymus Report of a Case I I Lemann, M D, and John Smith, M D, New Orleans	807
The Spectrophotometric Analysis of the Color of the Skin, and the Observa- tions by This Method in Normal and in Pathologic Subjects Charles Sheard, Ph D, and George E Brown, M D, Rochester, Minn	816
Book Reviews	832

INSENSIBLE PERSPIRATION ITS RELATION TO HUMAN PHYSIOLOGY AND PATHOLOGY*

FRANCIS G. BENEDICT, PH.D.

AND

HOWARD F. ROOT, M.D.

BOSTON

The changes that occur in the body weight from day to day or, indeed, from hour to hour are unnoticed by most persons, probably because the body weight is fairly constant for weeks at a time. Large losses in weight such as those which result from extreme exercise and profuse perspiration, as in athletic contests, are easily recognized, but smaller losses or increases are not so apparent. Thus, during the day variations in body weight amounting to several pounds, directly attributable to the ingestion of food and drink and the passage of feces and urine, may not be noted because it is not the custom to record the body weight frequently throughout the day and often the appliance on which the body is weighed is not accurate enough to show changes in weight of less than 1 pound or 0.5 Kg. Such alterations in body weight are easily understood, however, because they are visible changes. But the weight of the food and drink is not entirely compensated by the weight of visible excreta. There is also an invisible loss of gaseous substance in the form of carbon dioxide and water vapor, given off both from the lungs and the skin. This invisible loss may sometimes amount to 70 Gm. in an hour, even though the subject is quiet and resting. The share that these invisible, gaseous losses play in the twenty-four hour loss in weight is today but imperfectly appreciated, although it was considered of great physiologic importance three or more centuries ago.

Sweat can be seen and this visible perspiration can readily be perceived to represent a loss of material from the body. The invisible loss is not so readily recognized and a delicate balance must be relied on to establish it. The appearance on a cold, frosty morning of condensed

* From the Nutrition Laboratory of the Carnegie Institution of Washington and the New England Deaconess Hospital, Boston.

* This paper is no. 63 of a series of studies in metabolism from the Harvard Medical School and allied hospitals, the expenses of which have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

vapor in expired breath instantly shows, however, that such a gaseous loss is taking place. In addition, therefore, to the occasional and easily recognized changes in weight, such as the heavy losses experienced after severe muscular work (losses that may amount to 5 or 6 Kg. in an hour¹) and the decided changes in weight caused by disease or by dieting, attention must be directed to the continuous invisible or insensible losses that take place from the lungs and skin. If the body weight of a normal person not performing sufficient muscular work to produce visible perspiration is determined from hour to hour on good scales, it will be found to decrease steadily until food is eaten, when it will rise in accordance with the weight of food or drink taken. It will subsequently decrease at a fairly regular rate until urine or feces is passed, at which time the loss will be exactly that represented by the weight of the excreta. With increased activity, even if not carried to the point of producing visible perspiration, there is a greater loss in weight. With the reduced activity of rest in bed, the loss decreases but nevertheless persists. These changes in weight were strikingly shown in a series of weighings of a subject in the chemical laboratory at Wesleyan University.²

The uncertainty with regard to the exact nature of the loss in body weight is nowhere better brought out than in the innumerable expressions coined by different writers to express this loss. Thus, the earliest expression was "*perspiratio insensibilis*." Subsequently various terms were employed, such as "insensible loss," "intangible loss," "water vaporization from the lungs and the skin," and more recently the expression "hourly loss." On classical grounds and pending a more careful analysis of the nature and character of this loss (which the Nutrition Laboratory is now investigating, particularly with regard to the proportions of water lost from the lungs and the skin), the terms "*perspiratio insensibilis*," "insensible perspiration" and "insensible loss" will be used in this article as the most convenient terms available at the present time.

By "*perspiratio insensibilis*" is commonly meant those gaseous emanations from the body which do not appear in the form of sensible moisture or sweat, in other words, the insensible, invisible, intangible but weighable gaseous and vapor productions arising from the lungs in the process of exhalation and from the skin by due process of vaporization, i. e., excretion of moisture and carbon dioxide. The original idea of this classification was undoubtedly to distinguish the invisible from the visible loss of material from the body occurring when there is considerable perspiration.

1 Benedict, F. G., and Joslin, E. P. A Study of Metabolism in Severe Diabetes, Carnegie Inst., Wash., pub. no. 176, 1912, p. 96, table 114.

2 Benedict and Joslin (footnote 1, p. 91, table 111).

From the definition of the "perspiratio insensibilis" it is obvious that the experimental attack must be along certain definite lines. Since the interest lies in the total loss in weight of the body under conditions in which visible perspiration does not occur, the simplest method is, obviously, to weigh the body from time to time and note this loss. The simplicity of this operation, however, is far offset by the difficulties encountered. A balance of sufficient rigidity to support a man weighing 90 or even 100 Kg, and of sufficient accuracy to indicate a loss in weight which may average not far from 30 Gm per hour during a short period, is difficult to secure. Exactly this procedure has at times been followed in the past, however, and even in some of the most recent reports there are evidences of the successful use of a balance for determining this loss.

Quantitative physiologic measurements began, in a certain sense, with the determinations of the weight of the insensible loss, and the historical development of this problem reflects the development of the study of physiology. Indeed, unmistakable evidence of an understanding of the insensible loss of the body is shown in the classics of Hippocrates and Galen, a critical examination of whose writings has been made by Weyrich³. Since the research to be reported in this article represents a quantitative study of the insensible, gradual and continuous, though variable, losses in the body weight of human beings, exclusive of urine, feces, sputum and gross or visible perspiration, the researches of those earlier investigators who also made quantitative measurements of the "perspiratio insensibilis" should be at least briefly considered.

EARLIER QUANTITATIVE MEASUREMENTS OF THE "PERSPIRATIO INSENSIBILIS"

The first quantitative measurements of the insensible loss were made by Sanctorius⁴ in 1614, by means of an extremely ingenious steelyard. Suspended on a movable platform attached to this steelyard, he made innumerable measurements of his own loss in weight. Indeed, his records suggest that he carried these weighings out over a period of thirty years. Many of his curious aphorisms derived from findings with this balance have been quoted in the literature frequently, but obviously his conclusions are at present chiefly of historic interest, because he emphasizes the "perspiratio insensibilis". Some of his comments agree

3 Weyrich. Die unmerkliche Wasserverdunstung der menschlichen Haut, Leipzig, 1862.

4 Sanctorius. Medicina Statica, translated by John Quincy, Ed 2, London, 1720. Lusk, in his History of Metabolism, in Barker's Endocrinology, New York, 1922, 3 7, has reproduced a picture of Sanctorius suspended on his balance and has incorporated several of his aphorisms. Reference should also be made to King, J. T. Basal Metabolism, Baltimore, 1924, frontispiece.

and others disagree with present findings Sanctorius published no protocols and gives no idea of the sensitivity of his balance

The results of Sanctorius immediately stimulated a number of other investigators Among them was Dionysius Dodart⁵ (1634-1707) in Paris, whose observations likewise extended over thirty years and who pointed out a striking difference in the perspiration during the summer and winter Keill⁶ in 1730 made observations during a complete year and then at intervals over nearly a decade The work of Sanctorius and many of his followers is given in excellent abstract by Weyrich⁵ Reference should be made to Robinson,⁷ Rye⁸ and De Gorter⁹ of Europe and particularly to Dr John Lining of Charleston, S C, for as Weyrich points out, Lining's report was the most complete of any published up to that time

In 1740 Lining¹⁰ made an extensive series of observations on himself, which extended throughout the greater part of a year He weighed himself each morning immediately after rising and again at night, just before going to bed The balance used is not described, but according to the data reported it weighed in pounds, ounces and drachms The actual loss in weight is recorded in ounces and decimals of an ounce Although Lining's measurements were made nearly 200 years ago, his plan of study was comprehensive and merits attention today,¹¹ but because of the inherent inaccuracies in his method, his findings cannot be considered of great value His discussion deals chiefly with the influence of changes in season and the possible correlation between seasonal changes and the appearance of epidemic diseases in the South, which returned with great regularity at stated seasons Lining attributes

5 Dodart, Dionysius, cited by Weyrich *Die unmerkliche Wasserverdunstung der menschlichen Haut*, Leipzig, 1862, p 11

6 Keill *Tentamina Medico-Physica quibus accedit Medicina statica britannica* Lugd Batav, 1730 (Cited by Weyrich)

7 Robinson *Treatise of the Animal Economy*, Dublin, 1732, also Ed 3, London, 1738, *ibid* *Dissertation on the Food and Discharges of Human Bodies*, London, 1748 (Cited by Weyrich)

8 Rye Roger's *Essay on Epidemic Diseases*, Dublin, 1734 (Haller's *Bibl anatom*, II, 272) (Cited by Weyrich)

9 De Gorter *De perspiratione insensibili*, Lugd Bat, Ed 2, 1736 (Cited by Weyrich)

10 Lining *Philosophical Tr* 42 491, 1742-1743, 43 318, 1744-1745

11 One can hardly find a finer expression of the true research drive in an isolated individual, over three thousand miles from any great physiologic centers, than is given by Lining in the introductory paragraph of his first paper, in which he states "That candid and generous Principle which so universally possesses the Breasts of all true Friends to physical Literature, disposing them to give Assistance and Advice, even to such of the Illiterati who shew a Disposition of Inquiry after Truth, and that eminent Character you so justly bear in the Learned World, were sufficient Arguments with me, to lay before you, as a Specimen, one of my Meteoro-Statistical Tables The Favour of your Opinion of the Method I have observed, will be most acceptable"

to the changes in season a pronounced influence on the insensible perspiration.

Although numerous other researches bearing on insensible perspiration were published after the work of Lining, particularly by Home, Hartmann and Martin, the brilliant period in the development of physiology and chemistry is represented by the work of Lavoisier. Lavoisier and Seguin¹² in 1790 emphasized for the first time the importance of separating the cutaneous respiration from the pulmonary respiration, and the significance of the latter as a path for the loss of water vapor and carbon dioxide. The interest at the moment, however, lies in their observations on the total insensible loss in weight of a man, which they reported as ranging from 11 to 32 grains per minute. Thus, according to their data the man lost from 0.583 to 1.7 Gm per minute, or from about 900 to possibly 2,500 Gm in twenty-four hours. This loss represents both the "cutaneous respiration and the pulmonary transpiration and respiration."

Although he gave no details of his balance and its sensitivity, Colin¹³ in 1862 reported numerous measurements on himself made during repose and during activity. He found that his loss per hour, when he was quiet and asleep, varied from 28 to 30 and 35 Gm per hour. When he was awake his loss was 50, 60 and 80 Gm, increasing even to 200 Gm per hour with excessive exercise.

To study the insensible loss of fever patients, von Leyden¹⁴ in 1869 used a balance which had a capacity of 3 centner, with a sensitivity of 1 loth (about 10 Gm). His study is of interest as being the first in which a balance was used for pathologic cases.

In his classical study of the temperature of normal men, Jurgensen¹⁵ in 1873 likewise recorded the body weight with a balance to within 10 Gm. Unfortunately, he gives no description of his balance and does not give the weights of food and drink, so that the insensible perspiration may not be computed.

After a lapse of twenty-five years, when apparently no measurements of the "perspiratio insensibilis" were recorded in the literature, Dennig¹⁶ in 1898 reported the results of a careful study of the effect of reduction in the water intake. His series of values for the insensible perspiration

12 Seguin and Lavoisier. *Memoires de l'Academie des Sciences*, Paris, 1790 p 608, *Oeuvres de Lavoisier*, Paris, 1862, p 711

13 Colin. *Bulletin Société Imperiale et Centrale de Medecine Vétérinaire*, 1862, 7, ser 2, p 208

14 Von Leyden, E. *Untersuchungen über das Fieber*, *Deutsches Arch f klin Med* 5 308, 1869

15 Jurgensen, T. *Die Körperwärme des gesunden Menschen*, Leipzig, 1873, p 27

16 Dennig, A. *Die Bedeutung der Wasserzufuhr für den Stoffwechsel und die Ernährung des Menschen*, *Ztschr f diätet u physik Therap* 1 281, 1898

of the one subject with whom he worked range from 320 Gm per twenty-four hours on the sixth day of reduced water intake to 1,348 Gm on the second day. Since, however, the body weights could be recorded only to the nearest 100 Gm, these figures are liable to considerable error. On the days when the water intake was increased, the insensible loss ranged from 230 Gm on the first day to 1,065 Gm on the fifth day. A second experiment on the same person showed a somewhat different picture. Dennig concludes that when a subject undergoes a second period of reduction in water intake, he has to a certain extent become accustomed to the conditions. The actual values for the insensible perspiration are not recorded for this second experiment.

In studying three obese individuals, Dennig¹⁷ in 1899 again found considerable variability in the insensible perspiration from day to day. His protocols do not indicate that the daily activity was uniform, but variations as great as reported are difficult to explain on the basis of activity alone.

Using a balance reported as very sensitive, Bouchard¹⁸ in 1899 recorded a gain in weight of human beings amounting to from 10 to 40 Gm per hour, without any intake of liquid or solid material. This gain, he argues, is a convincing proof of the conversion of fat to carbohydrate. Bouchard's observations are of interest as an illustration of the use of the changes in total body weight rather than as proof of a transformation of fat to carbohydrate.

The use of an accurate balance to record the differences in weight from day to day was made about 1896 or 1897 by Atwater¹⁹ and his associates in connection with the respiration calorimeter at Wesleyan University, Middletown, Conn. The subjects inside the respiration chamber were weighed at certain times each day on scales, sensitive to 10 Gm. Since in these experiments there was a complete measure of the income and outgo, the data are at hand for computing the insensible perspiration, for not only were the food and the drink accurately weighed, but likewise the amount of water vapor given off and later the oxygen consumption. In May, 1897, and subsequently experiments were made in which the data were secured for computing the insensible perspiration. In one experiment, which lasted three days, records were made of the daily change in weight, the entire change in weight at the end of the three days, the total weight of food and liquid consumed, and the total weight of urine passed. The feces, unfortunately, were

17 Dennig, A. Die Bedeutung der Wasserzufuhr für den Stoffwechsel und die Ernährung des Menschen, *Ztschr f diät u physik Therap* 2 292, 1899.

18 Bouchard C. *Compt rend Soc de biol* 127 464, 1899.

19 Atwater, W. O., and Benedict, F. G. Experiments on the Metabolism of Matter and Energy in the Human Body, U. S. Department of Agriculture, Office Experiment Station Bulletin 69, 1899.

not collected until the end of the fourth day, and it is necessary to assume that since 502 Gm of feces were passed over a period of four days, 126 Gm were passed on each of the three days of the experiment. This same criticism applies to three other experiments made during this series. In one three day experiment and three four day experiments it was found that subjects living inside a respiration chamber had an insensible loss per day of 1,105, 1,180, 1,211 and 1,344 Gm, respectively. The round value of 1,200 Gm may be taken as the average for all four experiments. An insensible output of 50 Gm per hour was therefore found in the case of men living in the narrow confines of a respiration chamber (at a temperature of not far from 20 C, with a relative humidity of the air of usually not far from 50 per cent), doing no work but not confined in bed. It was the custom in all of the respiration experiments at Middletown, Conn., to have the data so recorded as to permit the computation of the insensible perspiration, but it is not until the twenty-four hour period is given up and shorter experiments are made that the most accurate data with regard to the insensible perspiration are available.

The method of weighing the body as a means of determining the insensible perspiration reached its acme of perfection in the development and construction of an extraordinary balance by Lombard²⁰ in 1906. This balance, which graphically recorded the changes in weight, was extremely sensitive, being the combination of a true balance with a spring scale. One side was overweighted by 3 or 4 Gm, so that as the man lost weight the spring contracted, drawing the arm of the balance upward. A writing point connected with the balance arm was in contact with a kymograph drum, giving a record of the weight lost in approximately two minutes. Lombard gives curves showing the great sensitivity of his apparatus, and likewise some curves showing the actual changes in weight of a man while resting on the balance. Two men, weighing approximately 70 Kg each, lost on the average about 40 Gm per hour. In another series of experiments when the temperature was considerably higher, the total loss amounted to nearly 70 Gm per hour, i. e., the loss was noticeably different with the same individual in a different environmental temperature. Professor Lombard²¹ has given us permission to use certain data on three healthy medical students who were measured in 1906 and 1907. His average values are summarized in table 1.

As the result of 107 observations Professor Lombard finds that in an average room temperature of 19 C the average loss in weight of

20 Lombard, W. P. A Method of Recording Changes in Body Weight which Occur Within Short Intervals of Time, *J. A. M. A.* **47** 1790 (Dec 1) 1906

21 Lombard, W. P. Recent personal communication to authors

these medical students was 41.5 Gm per hour. Professor Lombard also studied the loss from the air passages and from the skin alone. In the latter case he had each subject hold the breath for about twenty-seven seconds, during which time he noted the change in loss of weight on the balance. By this method he computes that the loss from the skin is about 24 per cent of the total loss. It is a matter of the greatest regret that this most promising, extraordinary piece of apparatus could not have been used further.

Zuntz, Loewy, Muller and Caspari²² in 1906 used an excellent balance, sensitive to 10 Gm, which was evidently in the laboratory at the top of Monte Rosa. Differences in body weights were determined daily, and the insensible perspiration was calculated by making corrections for the sensible income and outgo. Since their gaseous metabolism also was known, the authors were able to compute the loss from the lungs, thus dividing the total insensible perspiration between the lungs and the skin.

TABLE 1—*Insensible Loss in Body Weight of Healthy Medical Students (Lombard)*

Subject	Dates	Number of Observations	Body Weight, Kg	Height, Cm	Loss in Weight		Room Temperature, C
					Per Minute, Gm	Per Hour, Gm	
1	Nov 6 20, 1906	30	64.7	175	0.620	37.2	18
2	Jan 18 30, 1907	27	67.0	175	0.729	43.7	19
3	March 19 28, 1907	28	61.5	173	0.785	47.1	21
1	Nov Dec 1907	22	65.0	175	0.633	38.0	18
Average		107	64.5	175	0.692	41.5	19

Schwenkenbecher and Inagaki²³ in 1906, employing the method of weighing the body and all the intake and output of sensible material, in a series of experiments on two normal and eleven pathologic patients studied particularly the water exchange during fever. This research illustrates the practical use of the determination of the insensible perspiration in pathology. The body weight was apparently recorded only to within 100 Gm, but the experiments lasted approximately a week, so that the error was thus minimized. The two normal subjects showed water equilibrium in seven days. On the other hand, the fever patients showed a material water loss. The authors point out that this does not mean that there may not be an actual increase of water in the body.²⁴

²² Zuntz, N., Loewy, A., Muller, F., and Caspari, W. *Hohenklima und Bergwanderungen*, Ed. 1, Berlin, 1906, p. 377.

²³ Schwenkenbecher, A., and Inagaki. *Ueber den Wasserwechsel des fiebernden Menschen*, *Arch f exper Path u Pharmacol* 54:168 (Feb) 1906.

²⁴ Schwenkenbecher, A., and Inagaki. *Ueber den Wassergehalt der Gewebe bei Infektionskrankheiten*, *Arch f exper Path u Pharmacol* 55:203, 1906.

for the fever patients lost more organic body material than did the normal persons

In studying the influence of sodium chloride on metabolism, Tuteur,²⁵ in 1910, in Schwenkenbecher's clinic, obtained on himself an excellent series of twenty-four hour determinations of the insensible perspiration on sixty-one consecutive days, with reasonably uniform daily habits of life and diet. Most careful consideration was given to the weights of food, drink, urine and feces. The uniformity in his results from day to day is striking, especially since during the entire time he carried out his usual laboratory activities. Thus, the average loss per twenty-four hours during the first sixteen days was 1,474 Gm, during the next twenty days 1,429 Gm, during the next five days 1,655 Gm, during the next sixteen days 1,523 Gm, and during the last four days 1,578 Gm.

The twenty-four hour insensible perspiration was determined in 1910 by Caspari²⁶ in Durig's Monte Rosa expedition, in periods both of quiet and during marching. With the exception of one series of rest experiments, considerable variations were noted in the loss from day to day under seemingly the same conditions of activity. These variations are probably accounted for by the fact that the balance used by the author was, as he emphasizes, very unsatisfactory.

In an investigation on the relation of the loss of water from the skin and lungs to the external temperature, Osborne,²⁷ working in Australia in 1910 measured the loss in body weight by means of a very sensitive balance, called by him a "human balance," with which he claimed that the weighings were taken to the nearest gram. The experiments differed from the usual tests in that the balance was kept in a cool room in a wooden house about 20 yards from a hammock, suspended under a tree. In this series of experiments the subject was weighed very carefully, he then walked to the hammock and lay down quietly for an hour, when he was again weighed. All the measurements were made in the morning, covering a period of one hour. Occasionally a second experiment of one hour was carried out in the afternoon. Because of the very large differences in temperature (both of the dry and the wet bulb), the movement of air and the variations in the clothing worn, large differences in the loss of weight are recorded by Osborne.

25 Tuteur, R. Ueber Kochsalzstoffwechsel und Kochsalzwirkung beim gesunden Menschen, *Ztschr f Biol* **53** 361, 1910

26 Caspari, W. Ueber den Stoffwechselversuch in Alagna und uber die Einwirkung kurz/dauernden Aufenthaltes in grosseren Bergeshohen auf den Stoffwechsel, *Denkschr d math-naturwissensch Klasse d kaiserl Akad d Wissensch* **86** 483, 1910

27 Osborne, W. A. The Relation of Loss of Water from the Skin and Lungs to the External Temperature in Actual Climatic Conditions, *J Physiol* **41** 345 (Dec) 1910

Thus, in the rest experiments the hourly loss in weight varied from 362 Gm to as low as 44 Gm. In one experiment in which he chopped wood, the loss in weight was 840 Gm per hour. Walking in the shade produced in one instance an increase of about 100 per cent in the weight loss. Osborne also simultaneously measured and analyzed the expired air with a Zuntz apparatus.

Numerous experiments with subjects both at rest and during work were made by Benedict and Carpenter²⁸ in the Middletown calorimeter in 1910. The scales had a sensitivity of 10 Gm. Practically all the experiments were made at a uniform temperature of about 20 C, and the humidity was in general low. In the rest experiments the loss varied considerably, depending on the nature of the experiment, the size of the subject, and whether food was given or not, ranging from as high as 79 Gm per hour in a four hour experiment with one subject to as low as 23 Gm with another subject, at the end of a fast of about a week's duration. The results of all the rest experiments, representing 158 days and over 2,000 hours of observation, showed that the insensible perspiration of normal, healthy men while sitting, lying asleep or awake, or engaged in minor activities, is on the average 40 Gm per hour, with evidence of a pronounced influence of food and muscular activity. During severe muscular work the losses were much greater, about 200 Gm per hour, and in one case 276 Gm. Since, however, in these cases there was a large amount of visible perspiration, the comparison with the rest experiments, in which only invisible perspiration played a rôle, must be made with considerable caution.

Although they present no new data with regard to the insensible perspiration of either normal or pathologic cases, Benedict and Joslin²⁹ in 1912 included in their report on metabolism in severe diabetes a consideration of the changes in body weight which may occur throughout the twenty-four hours together with some discussion of the character and nature of these changes in weight, with special reference to the loss and gain of water by the body.

In connection with their expedition to the Alps, Galeotti and Signorelli³⁰ in 1912 determined their own insensible loss with an accurate balance (sensitivity 10 Gm) at the laboratory on the top of Monte Rosa. Using an average value for oxygen consumption previously determined by Zuntz and Durig, they also computed the loss from

28 Benedict, F. G., and Carpenter, T. M. *The Metabolism and Energy Transformations of Healthy Man During Rest*, Carnegie Inst., Washington, Pub. no. 126, 1910, p. 114.

29 Benedict, F. G., and Joslin, E. P. *A Study of Metabolism in Severe Diabetes*, Carnegie Inst., Washington, Pub. no. 176, 1912, p. 89.

30 Galeotti, G., and Signorelli, E. *Ueber die Wasserbilan während der Ruhe und bei der Anstrengung im Hochgebirge*, *Biochem. Ztschr.* **41** 268, 1912.

the lungs and that from the skin alone. They found considerable differences in the proportion of water lost from the lungs and skin, and from these findings drew conclusions with regard to the water balance.

Laying special stress on the loss in weight of the body and particularly during work, Boussaguet ³¹ in 1912 carefully determined the loss in weight, which he considered as due to loss of water. For these measurements he employed a balance which could weigh from 60 to 100 Kg with an accuracy of 5 Gm. His results, which unfortunately were not accompanied by metabolism measurements, showed considerable irregularity at times in the loss per hour during seemingly equal work. The effect of an movement was very pronounced. The air was excessively moist.

Ideal conditions for determining the insensible perspiration existed in a study of a fasting subject by Benedict ³² in 1915. The loss in body weight was determined on scales sensitive to 10 Gm, and records were kept of the weights of urine, feces and drinking water, so that the insensible perspiration was readily computed. Furthermore, since the fasting subject underwent a regular daily routine for thirty-one days, his losses from day to day are reasonably comparable. At the beginning of the fast the insensible loss was about 45 to 50 Gm per hour, falling off to an absolute minimum of 15 Gm per hour on the twentieth day of fasting, and rising again toward the end of the fast to 22 and 26 Gm per hour.

Emphasizing the importance in the clinic of a knowledge of the insensible perspiration, Isenschmid ³³ in 1918 pointed out that the insensible perspiration is equal to the weight of the water given off, plus the weight of the carbon dioxide given off, minus the weight of oxygen consumed. From the diet one can compute the amount of carbon dioxide produced and the oxygen required to oxidize the food. Hence, if the subject is in metabolic equilibrium, one can compute in this way the insensible water loss.

In practice in the clinic Krehl ³⁴ in 1919 made use of measurements of the insensible perspiration, particularly in studying disturbances in water balance and in the use of digitalis. His balance was not very sensitive, having an accuracy only of from 50 to 100 Gm, but he states that the method of determining the insensible loss from body weights and weights of urine and feces has been employed in his clinic for many

31 Boussaguet. *Recherches expérimentales sur les conditions physiologiques du travail des mineurs*, Paris, 1912.

32 Benedict, F. G. *A Study of Prolonged Fasting*, Carnegie Inst., Washington, pub. no. 203, p. 84, 1915.

33 Isenschmid. *Die Bestimmung der Wasserbilanz am Krankenbett*, Med. Klin. **14** 1128, 1918.

34 Krehl. *Zur Kenntnis des Digitalisgebrauchs und des Wasserwechsels*, Deutsches Arch. f. klin. Med. **128** 165, 1919.

years This measurement was entirely aside from the daily weighing of the patient to control the water intake

The pathologic significance of the insensible perspiration of children played a considerable rôle in Nobel's³⁵ discussion in 1919 of the importance of limiting the water output by diet Nobel, in Pirquet's clinic, in Vienna, determined the insensible perspiration indirectly from the weight of the body and the weight of the intake and output, but gave no computations

In studying the energy requirements of numerous groups of girls from 12 to 17 years of age, Benedict and Hendry³⁶ in 1921 determined on scales sensitive to 10 Gm the weight of each girl just before going to bed and on rising in the morning Six different groups, each including eleven or twelve girls, were studied during the night while sleeping in a respiration chamber at a temperature of about 20 C, with 40 per cent relative humidity The average insensible perspiration per person during the night was found to be 38, 31, 32, 45, 34 and 32 Gm per hour, respectively On the basis of a kilogram of body weight the loss averaged from 0.63 to 0.93 Gm per hour, with no evidence of any influence of slight differences in humidity

Two other groups of girls, 18 and 14 years of age, respectively, were also studied by Benedict³⁷ in 1923 The measurements were made during an eight hour period at night in the respiration chamber, and the insensible perspiration for each group was found to be essentially the same, namely, 33 Gm per hour Individual losses ranged from as low as 18 Gm to as high as 45 Gm per hour

In a consideration of pneumonia in infants, Meyer³⁸ in 1923 made use of the insensible perspiration determined by a balance which had a sensitivity of from 1 to 2 Gm Since he found that the loss in weight was only from about 8 to 15 Gm per hour, the error with this balance was large and he therefore had another balance constructed which was capable of weighing 15 Kg to within 0.1 Gm With this balance, although it took half a minute to secure equilibrium and the child might lose 0.1 Gm during this time, Meyer states that he could weigh the loss during ten minutes with a precision of about 5 per cent All the work was done with children, and usually in a fairly standard environment In one typical case the loss was 7 Gm per hour when the child was

35 Nobel, E Ueber den Wasserhaushalt des kindlichen Organismus, die Grenzen der Wasserentziehung und ihre systematische Anwendung bei pathologischen Zuständen, *Ztschr f Kinderh* **22** 1, 1919

36 Benedict, F G, and Hendry, M F The Energy Requirements of Girls from Twelve to Seventeen Years of Age, *Boston M & S J* **184** 217, 257, 282, 297, 329 (March) 1921

37 Benedict, F G The Basal Metabolism of Young Girls, *Boston M & S J* **188** 127 (Feb) 1923

38 Meyer, Jean La broncho-pneumonie du nourrisson, Paris, 1923

asleep, 10 Gm when he was awake and quiet, and 14 Gm when agitated and crying. He also found that generally there was an increased loss immediately after feeding, but subsequently a rapid decrease. He studied the factor of clothing, and also made some experiments with nude infants. These experiments were difficult to carry out. They were usually accompanied by a pronounced fall in rectal temperature, and occasionally the children were cold and moved about considerably. The removal of clothing apparently had little effect. Temperatures from 18 to 23 C were without significance, but above 23 C there was a somewhat larger loss. He concludes that humidity has little, if any, effect, although his evidence is based on only one experiment. Finally, he considers that the twenty-four hour loss, calculated from weighings on the balance over a period of two hours, has a significant relationship to the total intake of water in food and drink, a relationship that is of real clinical assistance. Thus, the normal relation of the twenty-four hour loss of water to the total intake of water is 42 per cent. In a case of eczema the relationship was 50 per cent, with an atrophic infant it was 54 per cent, while with three "hypotrophiques débiles" the ratio was from 24 to 34 per cent.

In 1925 Meyer³⁹ made practical use of the insensible perspiration in treating cases of eczema by the milk diet, as he considers that the withholding of water is an important factor in treating eczema.

Just after completing our manuscript, we received from Dr. Meyer further measurements⁴⁰ of the insensible perspiration of infants, evidently made with the same scales that he used in 1923. Meyer concludes that under conditions of repose and with an environmental temperature of about 18 C the hourly insensible loss is approximately 40 centigrams per square decimeter of body surface, whether the subject studied is a small animal, like a guinea-pig, an infant or an adult man. He therefore believes that the insensible perspiration obeys a law comparable to that which governs the expenditure of heat, that the study of the insensible perspiration is accordingly related to the study of nutrition, and that this study may result in new findings in certain chapters in the pathology of the infant and seems capable of certain clinical applications.

In studying the influence of protein and carbohydrate on the heat production in a continuous bath at 37 C, Schmitt⁴¹ in 1925 noted the pronounced effect of protein on the insensible perspiration as compared

39 Meyer, Jean. *Revue française de dermatologie et de vénéréologie*, April and May, 1925.

40 Meyer, Jean. *La perspiration de l'eau chez le nourrisson*, *Rev. franç. de Pédiat.* **1**:409, 1925.

41 Schmitt, W. *Neue Untersuchungen über Eiweisshyperthermie*, *Jahrb. f. Kinderh.* **107**:181, 1925, *Weitere Untersuchungen über die Entstehung der "dynamischen Eiweisshyperthermie"*, *Arch. f. exper. Path. u. Pharmacol.* **106**:89, 1925.

with that of sugar, the insensible perspiration being almost twice as great, that is, 725 Gm in six hours with sugar and on the average around 1,700 Gm with plasmon and meat. No respiration experiments were made. Since the body was in a saturated atmosphere, the absolute values for insensible perspiration may be questioned. It is of importance, however, to note that the author considers the difference in the insensible perspiration as being an indication of the difference in metabolism. The difference between the effect of the ingestion of protein and sugar was noted under identically the same conditions, however, and may be taken as an excellent indication of the well known, striking increase in the metabolism following the ingestion of meat, as compared with that following the ingestion of sugar.

NATURE OF THE INSENSIBLE PERSPIRATION

Based on the literature (not only that cited in this paper but likewise the extensive literature treating of the amount of carbon dioxide lost from the skin, and the water vapor lost from the skin as distinguished from that lost from the lungs) and on a large amount of unpublished material in hand at the Nutrition Laboratory, a general statement with regard to the nature of the insensible perspiration may be made at this point, although experimental treatment of this subject is now being made.

The insensible perspiration deals with the gaseous emanations from the lungs and skin. These emanations are, in the case of human beings, chiefly carbon dioxide and water vapor, for the amount of marsh gas produced is relatively so small that it may be disregarded. Of the carbon dioxide a small amount (approximately 1 per cent of the total) leaves through the skin and the rest leaves through the lungs. The greater proportion (around 85 per cent) of the insensible perspiration however, is represented by water, vaporized both from the lungs and the skin. Furthermore, the oxygen absorbed by the lungs plays an important rôle in the insensible perspiration. When oxygen is used to burn carbonaceous material, it escapes in the carbon dioxide and obviously is cancelled in the balance between income and outgo. When it is used to burn hydrogen, the water formed may be excreted, but undoubtedly simply goes into the large pool of water in the body. For every gram of hydrogen burned 8 Gm of oxygen is required, and in this case there is an actual addition to the water of the body, unless one assumes that the water thus produced is immediately lost from the body. On the other hand, when carbonaceous material is burned, the carbon of the carbon dioxide given off represents a true body loss. The innumerable

measurements of human metabolism indicate that the average man or woman, while resting, loses from the body each hour about 6 or 5 Gm of carbon, respectively, and until further refinement of these values is justified these two figures may be accepted as correct. From an examination of the earlier literature it is obvious that the total average hourly loss in weight ranges from 25 to 40 Gm. The 5 or 6 Gm ascribable to carbon of carbon dioxide represent, therefore, but a small fraction of the total loss, and the only other factor that enters into the insensible loss to any great degree is that of water. The almost generally synonymous use of the terms "insensible perspiration" and "water vaporized from the body" is thus reasonably justified.

PLAN OF PRESENT RESEARCH

The development in recent years of large respiration chambers, permitting the complete measurement of the gaseous exchange, that is, the determination of the carbon dioxide produced, the water vaporized, and particularly the oxygen consumed, makes it possible to compute the insensible loss indirectly, for the weight of the water vapor given off, plus the weight of the carbon dioxide produced, less the weight of the oxygen absorbed, is essentially the insensible loss from the body. The practical difficulties surrounding the chamber method, the necessity for close confinement of the subject, and the length of time required for the period of observation, led to the attempt to measure the insensible loss by simpler means without undue confinement or restriction. Evidence has been accumulated to suggest that there is a sufficient degree of correlation between the insensible loss and the metabolism to make the measurement of the insensible loss of direct practical value. With this in mind we began our research.⁴² The technic was first improved by increasing the sensitivity of the measurements and then shortening the period of observation, so that successive periods of observation could be made and each period used as a control on the preceding one. Finally, the observations were extended into the field of pathology, since relatively appreciable alterations can take place in the metabolism of a pathologic subject, even when resting. Thus, it was possible to study more intimately the correlation between the insensible loss and the metabolism. Evidence of a relationship between muscular activity and insensible loss appears continually in the literature. In the earlier work of the Nutrition

⁴² Benedict, F. G. The Correlation Between Perspiratio Insensibilis and Total Metabolism, Collection of Articles Dedicated to the Seventy-Fifth Birthday of Prof. I. P. Pawlow, Published from the Institution of Experimental Medicine in Leningrad, 1924, p. 193, *Nouvelle recherches du "Nutrition Laboratory" de Boston sur le métabolisme de l'Homme et des animaux*, Bull. Soc. Sc. d'Hygiène Aliment. **11** 343, 1923, *Grundumsatz und perspiratio insensibilis nach neuen Untersuchungen*, Schweiz. med. Wchnschr. **53** 1101, 1923.

Laboratory and that at Wesleyan University the relationship seemed close. Since the metabolism may be considered as the best measure of muscular activity, and particularly the best measure of vital activity, even when no external muscular work is performed, it was decided that a study of the insensible perspiration and its relation to the metabolism of normal and pathologic subjects, particularly with simultaneous measurements of the metabolism and the insensible perspiration, would be of both physiologic and pathologic importance. This investigation therefore took place in two parts. The physiologic study was carried out at the Nutrition Laboratory. This included the measurements of the insensible loss of a number of normal individuals and subsequently an analysis of the nature of this loss by determining the loss from the skin separately from that from the lungs. The pathologic study was in part carried out by bringing the ambulatory patients to the Nutrition Laboratory and weighing them there on a delicate balance. Subsequently, a delicate balance was installed at the New England Deaconess Hospital, where a large number of pathologic patients also were studied. As the research progressed, the measurement of the metabolism at essentially the same time as that of the insensible perspiration and under the same conditions was also included in the experimental program, whenever possible.

METHODS

Platform Scales—Preliminary observations were made with platform scales, the so-called "silk scales," such as were used in the researches at Wesleyan University, Middletown, Conn., and at the Nutrition Laboratory with a fasting man. These are manufactured by at least two large scale manufacturing concerns and are designed to weigh about 150 Kg., the scale beam being divided into "10 Gm." divisions. Two forms exist, one with a low and one with a high pillar or post. For convenience in weighing, the high post is preferable. Manufacturers have announced their willingness to supply a traveling weight which would indicate 5 rather than 10 Gm. In figure 1 an illustration of the platform scales is given.

Highly Sensitive Balance—Although we could not hope to secure a balance having the accuracy and sensitivity of that marvelous instrument perfected at the laboratory of Professor Lombard,²⁰ we were fortunate in finding a large balance manufactured by August Sauter at Ebingen, Wurttemberg, Germany. This manufacturer furnishes a number of balances of special construction, the largest of which has a capacity of 100 Kg. on each arm. The Nutrition Laboratory has numerous forms of this balance in several sizes and finds that it is invariably more sensitive and has a larger capacity than the manufacturer

claims Benedict and Carpenter⁴³ attached a 100 Kg Sauter balance to one of the respiration chambers and made it possible to weigh a man suspended on a chair inside the respiration chamber. With this balance it was possible to weigh the subject to within from 0.1 to 0.3 Gm. Since the carbon dioxide produced and the water vaporized were simultaneously measured, it was possible to compute the oxygen consumption indirectly from the actual measurements of the change in body weight, the total water vaporized, and the carbon dioxide produced.⁴⁴

The inherent difficulties of securing a high degree of accuracy when weighing a subject inside a closed respiration chamber and of providing for an air-tight enclosure between the balance and the suspension rod

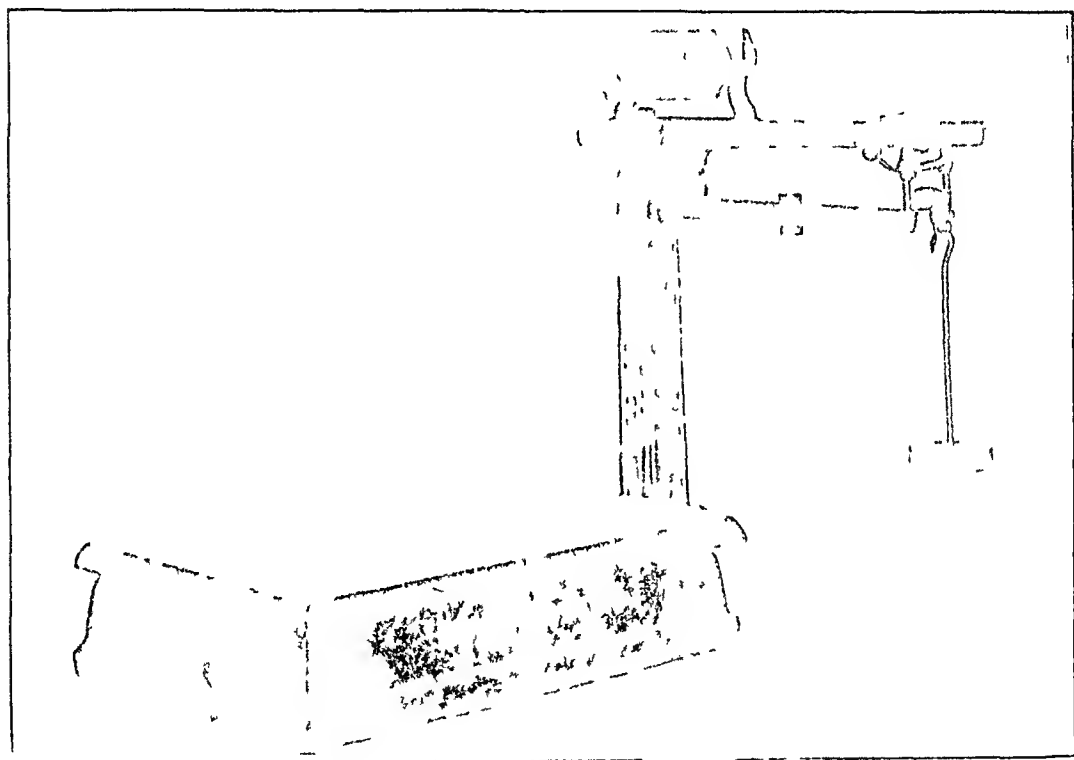


Fig. 1—Platform scales, so-called "silk scales," sensitive to 10 Gm

made it impracticable to use this balance for a general study of the insensible perspiration. Subsequently, it was installed in a special room and arrangements were made so that the subject could either sit in a chair or lie on a comfortable suspended spring mattress. Observations therefore began anew on this problem in 1921.⁴⁵ The whole apparatus

43 Benedict, F. G., and Carpenter, T. M. *Respiration Calorimeters for Studying the Respiratory Exchange and Energy Transformations of Man*, Carnegie Inst., Washington, Pub. no. 123, 1910, figures 4 and 9.

44 Benedict, F. G. A Comparison of the Direct and Indirect Determination of Oxygen Consumed by Man, *Am. J. Physiol.* **26**:15 (April) 1910.

45 Benedict, F. G. Nouvelles recherches du "Nutrition Laboratory" de Boston sur le métabolisme de l'Homme et des animaux, *Bull. Soc. Sc. d'Hygiène Aliment.* **11**: 356, 1923, figure 4.

was demonstrated at the Carnegie Institution of Washington at Washington, D C , at a conversazione in December, 1923 The successful use of the balance with its suspended spring bed, not only with normal subjects but with a certain number of pathologic cases at the Nutrition Laboratory, made it imperative to install a similar balance in a hospital ward A second balance was therefore secured from Germany and mounted in the basement of the New England Deaconess Hospital (fig 2) in the spring of 1925, where often four subjects were weighed in the course of one day

Obviously, the balance must be well mounted This has been accomplished by making a rigid support of two upright planks, 12 inches wide, 2 inches thick and about 11 feet long, i e, 31 by 5 cm by 34 meters These planks are attached at right angles to each other so as to form a bridge or backbone, and tightly wedged in a true perpendicular position between the ceiling and the floor of the laboratory room The balance itself rests on a cast iron angle or base, bolted securely to this upright frame The top of the balance is also fastened to the upright, so that the greatest degree of rigidity is secured and the apparatus is plumb A fine mesh woven wire cot bed, with the sides turned up from 8 to 10 cm to hold the bedding securely in place, is suspended on one arm of the balance On the other arm provision is made for the addition of a large amount of lead or other heavy material as a counterpoise Finally, a small pan is provided over the bed so that small weights can be added or subtracted quantitatively from this pan Owing to the large weight suspended (often 200 Kg) on the balance, it has been found advantageous to raise and lower it by means of a worm gear, the turning of which slowly raises or lowers the balance arm as the operator wishes Efficiency in its use has been rapidly acquired by a number of untrained workers

The cooperation of the subject is essential, particularly during the moment when the balance is being suspended and the exact point of equilibrium is being secured The loss in weight of the body is so continual that it is impossible to secure any exact weight for any stipulated moment That side on which the bed is suspended is, therefore, slightly overbalanced, and the operator then waits until the loss of weight of the subject equals the weight on the counterpoise, when the time is accurately noted on a watch From the time between the weighings, as thus noted, and the actual differences in weight, the loss in weight during fifteen minutes or an hour may readily be calculated Weighings are ordinarily made every ten or fifteen minutes, and from six to twelve weighings secured, which serve as controls on each other

Both the "silk scales" and the sensitive Sauter balance were selected for the study of the insensible perspiration, since it was believed that

by then use the most normal conditions possible could be secured in the hospital ward. From the standpoint of the patient, therefore, the environment is a normal one, as no confining or restraining appliances are necessary.

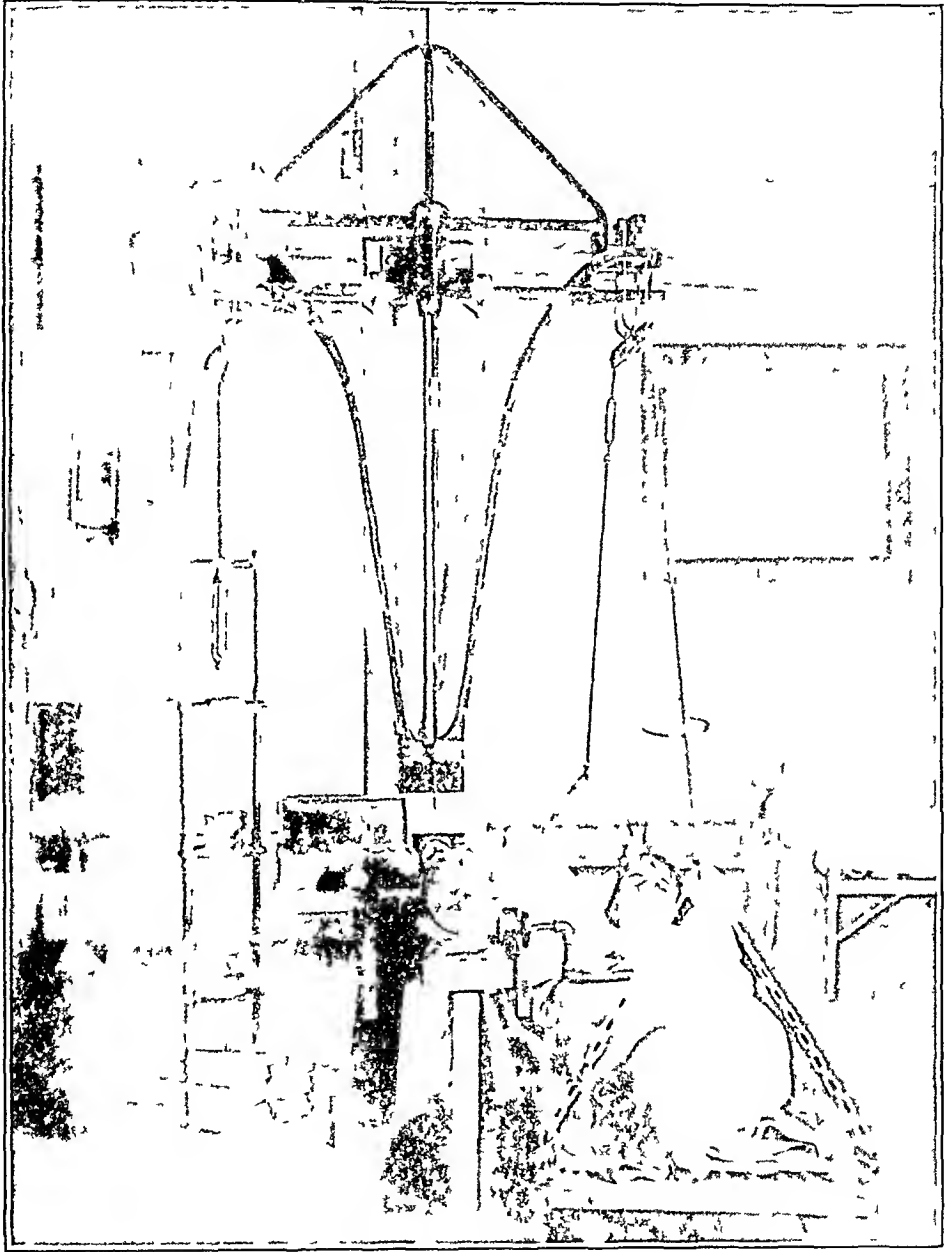


Fig 2—Installation of 100 Kg balance with suspended bed and counterpoise in the New England Deaconess Hospital. The worm gear for raising and lowering is in the foreground, a small circular pan is attached to the support over the bed, and in it are placed weights corresponding to the loss in weight of the subject.

With these two methods equally satisfactory results were obtained. When the silk scales, which have a sensitivity of 10 Gm, are used, the period of measurement is lengthened to cover several hours, so that the total loss in weight will be of such a magnitude that the error in weighing is not significant. Usually an eight or ten hour experiment

is amply sufficient. One difficulty in these long experiments is the possibility of overlooking the slight additions to or deductions from the weight of the body caused by the dropping of a hairpin, the changing of a wrist watch, or even the removal of a set of teeth, as well as by the drinking of water, the taking of medicine, or the passing of urine or feces. If such additions or subtractions are carefully noted, however, and suitable corrections are made in the computation of the true loss in weight, the accuracy is all that could be desired and the method is practicable for a hospital ward. When the silk scales are used, the weight is determined only over one long period, for example, at the beginning of the night and again the next morning. Correction for error in either weight cannot be made, and in order to secure a duplicate value for a check another experiment of approximately eight hours must be made the following night. The advantage in using the balance with a high degree of sensitivity is that the subject is continually under surveillance, from six to twelve weighings are secured in a relatively short time, and an aberrant weight is instantly noted if the values for the weights are plotted in relation to the time. Obviously the cost of the "silk scales" is small, amounting to thirty or forty dollars. The balance will cost approximately \$200, and the labor of mounting it with worm gear perhaps another hundred dollars, depending on the skill of the person mounting the apparatus.

RESULTS

Preliminary Overnight Experiments with Platform Scales—Although the experiments with these scales (sensitivity 10 Gm) at Wesleyan University indicated that results of value could be obtained with them, further tests of the method were made by a member of the laboratory staff (T M C) and his wife (K M C) in intermittent observations at their home during a period covering the greater part of a year. The subject, T M C, who weighed 53.5 Kg, found as an average of thirty weighings during periods at night of eight hours each, that his hourly insensible loss was 27.4 Gm. The normal woman, K M C, whose average weight was 60 Kg, had for sixty-four nights an average hourly insensible loss of 28.7 Gm. The variations from these average values were occasionally large, but since the balancing of the scale arm and reading of weights were uncontrolled, the results may be considered to be reasonably uniform. When the readings are unchecked, however, it is only the general picture of such preliminary observations that can be considered. To be accurate, the weighings should obviously be made by another person, as it is difficult for the subject to adjust the balance when squatting down, and still more difficult to read it accurately.

A second series of overnight weighings with the platform scales was made by the normal subjects H K R and H F R and gave more uniform results. The average loss of the woman, H K R (average body weight 55.5 Kg), during five consecutive nights amounted to 24 Gm per hour, with great regularity from night to night. Prior to this series measurements on another set of scales, which were unsatisfactory, showed great variability in the loss of weight and also larger losses, averaging 30 Gm per hour. In this series, however, the subject had taken a warm bath each night just prior to the weighings. It is reasonable, therefore, to believe that the skin was surcharged with water and that the larger loss noted on these nights was due to the effect of the bath. The man, H F R (average body weight 74.5 Kg), had an average loss of 29 Gm per hour on four different nights.

The only conclusions to be drawn from these preliminary overnight observations on normal subjects are that in general the loss is approximately proportional to the body weight and that with extra precautions fairly uniform values on successive nights can be secured.⁴⁶ In the earlier observations of F G B and C G. B.⁴⁷ it was noted that on those nights when the subjects slept very quietly the loss was much less than on nights when there was considerable restlessness. This fact would indicate that muscular activity results in a larger loss.

On the basis of these preliminary experiments this method was put into use at the New England Deaconess Hospital, but special care was taken to adjust the balance beam accurately at each weighing, to read the weights carefully, to take an inventory of the clothing and other appurtenances worn at the time of the initial weighing, to record the time and amount of any intake of drink or food and any passage of urine or feces, and to make sure that the clothing was the same at the time of weighing on the following morning. Under these conditions, particularly when the situation was not complicated by the drinking of water or the passing of urine, an extensive series of observations was made at the hospital on thirty-two diabetic patients. Duplicate experiments,

46 The significance of these overnight experiments was pointed out by one of us in a lecture at the University of Hamburg in June, 1923, and Professor Kestner, with characteristic energy, immediately had a number of balances placed in different wards of the hospital. The next day, however, he stated that their observations had failed to confirm the prediction of a general correlation between insensible loss and body size, the simplest index of metabolism. This was somewhat surprising, since Professor Kestner himself had made very practical use, in studies on the water balance in the body, of determinations of the loss overnight, and had reported an interesting series of nine to ten hour overnight losses, ranging in his own case from 211 to 360 Gm (Sohnheim, O., Kreglinger, and Kreglinger *Beitrage zur Physiologie des Wassers und des Kochsalzes*, *Ztschr f physiol Chem* 63 420, 1909).

47 Benedict, F G., and Joslin, E P. *A Study of Metabolism in Severe Diabetes*, Carnegie Inst., Washington, Pub no 176, 1912, p 91.

usually on consecutive nights (in one instance five nights), showed a singular uniformity in the loss of weight per hour

SHORT EXPERIMENTS WITH A HIGHLY SENSITIVE BALANCE

It was essential at the outset to study two important problems, *i e*, whether the insensible loss in weight is regular from night to night and whether it is regular from hour to hour. Obviously only the first of these questions could be answered by overnight measurements. But to determine the regularity in the hourly loss it was necessary to employ a highly sensitive balance, which would permit from six to ten accurate measurements during a period not of eight hours but of one hour or two hours. The large, sensitive Sauter balance was therefore mounted in a special room in the Nutrition Laboratory in the fall of 1923, and various members of the laboratory staff were weighed in periods varying in length from thirty minutes to an hour, at intervals of about ten minutes.

FACTORS AFFECTING THE "PERSPIRATIO INSENSIBILIS"

During the observations in 1923 factors which are now known to have a pronounced influence on the insensible perspiration were, through ignorance, entirely disregarded. Thus, the influence of the character and the amount of food eaten prior to the test and the length of time that elapsed following the meal were ignored. To be sure, precautions were taken not to make experiments on rainy or snowy days when the subject's clothing, particularly the shoes and stockings and the lower part of the trousers or skirts, would be wet. But it is undoubtedly true that in certain instances the face and hands had been washed and the hair had been wet just prior to the tests, for the members of the staff were frequently called from their regular work at almost any hour of the day to serve as subjects on the balance for one or two hours. The after-effect of climbing the three flights of stairs to the room where the balance was installed, and any psychical effect (these being especially to be found in pathologic cases) were also too often overlooked. Thus, the data were secured under conditions that could not at the present day be considered as ideally comparable.

Body Size and Sex—The values for the insensible loss of these normal subjects, as noted in experiments lasting from thirty minutes to two hours, are tabulated in table 2, in the order of increasing body weights. An inspection of this table shows that in general the smaller body weight is accompanied by a small insensible loss, and that the largest insensible losses occur with those subjects having the largest body weights. Another factor, however, should be considered in the interpretation of these figures, *i e*, the possible influence of sleep, since unavoidably in some instances the subjects were asleep. The losses

recorded in this table may therefore be affected by the factors of food, sleep, exercise, psychic apprehension and moisture on hair, hands and face, and for this reason the only definite conclusion that can be legitimately drawn from these data is that in general the larger insensible loss occurs with the larger body weights

Food—In all the measurements reported in table 2 the subjects were quiet but had eaten food. Since it was known that food and changes in body position or slight muscular activities result in an increased metabolism, preliminary observations were made with normal subjects on the influence of these factors on the insensible loss. From the data in table 3 it is obvious that following the ingestion of food (amount and character of food not recorded) there is invariably an increase in the insensible loss.

TABLE 2—*The Insensible Perspiration of Normal Persons During the Day*

Subject*	Body Weight (Nude), Kg	Insensible Loss per Hour, Gm
1	36.5	19.5
2	42.5	21.0
3	44.5	18.0
4	48.5	19.0
5	50.5	28.5
6	52.5	30.5
7	59.3	28.5
8	60.0	22.0
9	60.0	28.0
10	60.3	20.0
11	62.0	28.5
12	63.1	36.0
13	63.3	32.5
14	66.0	30.0
15	67.2	30.0
16	73.3	26.0
17	78.0	30.0
18	77.2	29.5
19	89.0	33.0
20	90.5	44.0

* Subjects 2, 3, 4, 8 and 10 were women, all the others were men

Exercise—The effect of moderate exercise involving a change in position from lying to sitting, and the effect of more vigorous exercise, such as walking, calisthenics or riding on a bicycle ergometer, were also studied with normal subjects. In a series of experiments with seven subjects, in which the influence of a change in position from lying to sitting was studied (unfortunately the two positions were studied on different days), an increment in the insensible loss when the subject was sitting was invariably noted. This increment amounted generally to about 5 Gm per hour. In the case of two men who walked vigorously around the room for ten minutes, the loss (computed on the hour basis) rose from 33 Gm while the men were lying quietly, to approximately 60 Gm. A woman, who exercised in calisthenics for fifteen minutes, increased her insensible loss from 25 Gm per hour (lying) to 43 Gm. In a few experiments in which a subject rode a bicycle ergometer

vigorously until visible perspiration appeared, there were very great increases in the loss, amounting to 500 and 600 per cent, or even more. Since, however, the plan of this research was to study the insensible loss prior to the onset of visible perspiration, the details of these experiments with the bicycle ergometer are reserved for later publication.

RELATIONSHIP BETWEEN "PERSPIRATIO INSENSIBILIS"
AND METABOLISM

The conclusion that there is a general tendency for the insensible loss to be greater with larger weights and with increasing activities, coupled with the fact of the well known relationship between body size, body activity and metabolism, immediately suggested the possibility of a relationship between the insensible loss and the metabolism. To determine whether such a relationship exists it would be ideal to carry out a series of observations on normal subjects which should include the measurement of the insensible perspiration and immediately thereafter the measurement of the basal metabolism. Few normal subjects were studied in

TABLE 3—*Influence of Food on the Insensible Perspiration of Normal Subjects*

Subject	Loss per Hour	
	Before Food, Gm	After Food, Gm
Men		
7	28.0	32.4
14	27.3	34.6
15	33.0	36.5
17	29.5	33.4
19	34.4	39.0
Women		
2	20.9	24.4
8	16.8	21.2

this way, however, for it became possible, thanks to the cooperation of Drs. E. P. Joslin and F. H. Lahey, to make this comparison with diabetic and thyroid patients at the New England Deaconess Hospital. Because of the marked difference between the metabolism of the diabetic patient, whose chief object in life is to conserve heat, and the metabolism of the toxic goiter patient, whose chief object in life is to lose heat, it was believed that a series of observations on these two types would furnish the best evidence as to the possible relationship between insensible perspiration and metabolism. Accordingly, a relatively large number of both types of patients were studied, and the loss in weight was measured just prior to the determination of the metabolism.

In figure 3 are plotted the results of such measurements on the diabetic and thyroid patients, the insensible perspiration (expressed as grams per hour) being represented by the ordinates and the heat production for twenty-four hours (as computed from the determined oxygen

consumption) by the abscissas. The thyroid patients are indicated by dots and the diabetic patients by small crosses.

Although the scatter of the plotted points makes the laying on of a straight line curve debatable, nevertheless since it is not materially greater than the scatter in many charts in which curves have been drawn for the prediction of the metabolism, such a curve has been drawn in figure 3 in accordance with the custom of the Nutrition Laboratory in preparing smoothed curves.⁴⁸ This curve shows that there is a reasonably close relationship between the insensible perspiration and the measured metabolism.⁴⁹ As is to be expected, the diabetic patients have in general the lower metabolism, the crosses representing the diabetics being, with few exceptions, at the lower, left hand side of the chart. The numerical scatter of the crosses above and below the straight line is essentially uniform. The dots representing the thyroid patients extend to the upper part of the curve, indicating their great heat production. The comparison made in figure 3 obviously does not introduce the element of size (either height, weight or surface area) or of age, for the problem is to note whether there is any correlation between the loss of weight and the production of heat, irrespective of the size of the subject.

INFLUENCE OF ENVIRONMENTAL TEMPERATURE OR SKIN TEMPERATURE

In this series of observations aberrant figures were not infrequently found, especially with the thyroid patients, and the protocols showed that in such instances there was invariably visible perspiration. These data were not plotted in the chart. In a number of cases it was also observed that the points lying well below the line, toward the outer scatter, represent experiments in which the temperature of the room or the prior exposure of the subject was such as to lead to the belief that the subject was *cold*. Here for the first time was the significant influence of environmental temperature clearly recognized.

48 Benedict, F. G. Physical Factors in Predicting the Basal Metabolism of Girls, *Proc. Am. Philosophical Soc.* **63**, 31, 1924.

49 Belief in the relationship between insensible perspiration and metabolism is strongly supported by the striking observations of Prof. E. G. Ritzman of the Institute of Animal Nutrition at the University of New Hampshire. In his experiments it has been found that when the insensible perspiration and simultaneously the metabolism of adult steers (weighing 600 Kg.) are carefully determined, changes in the insensible perspiration are closely related to changes in the total metabolism. Thus, a large steer on full ration, producing about 16,000 calories per day, had an insensible perspiration of approximately 16 Kg. After a period of prolonged submaintenance feeding, when the animal had adjusted itself to its lower nutritive plane and the metabolism had fallen to approximately 8,000 calories per day, the insensible perspiration was not far from 6 or 7 Kg per day.

Most of the studies on normal subjects had shown seemingly little, if any, influence of environmental temperature on the insensible perspiration. Indeed, the act of disrobing and subjecting the body to a blast of room air from a strong electric fan frequently did not alter in the slightest the insensible loss. A series of experiments was then planned with normal subjects, to study simultaneously the insensible perspiration and the metabolism, first, when the environmental temperature was low (16 or 17 C), then when the temperature was increased 5 degrees, and again when it had been increased still another 5 degrees. Under these conditions the subject was at the start of the experiment cold, or, in the last analysis, the actual skin temperature was low. Thus, this

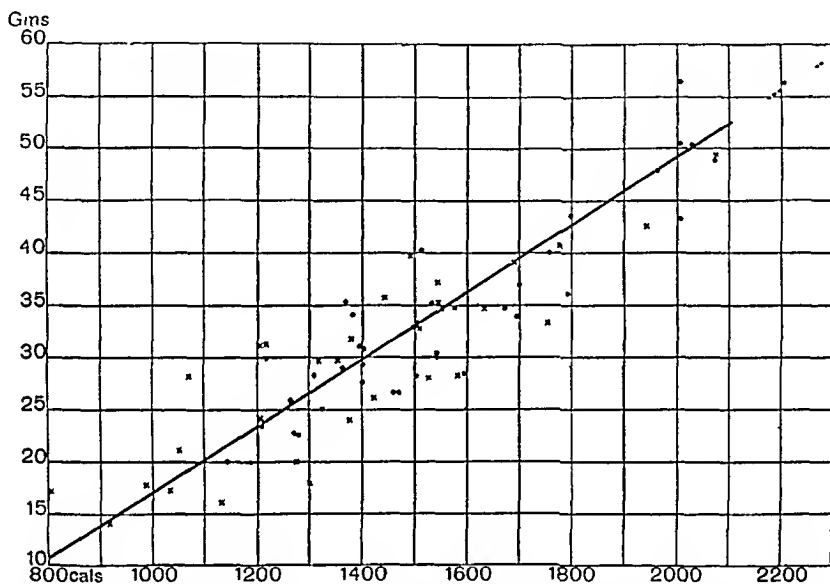


Fig 3—Relationship between the insensible perspiration per hour and the simultaneously measured heat production per twenty-four hours of a group of diabetic and thyroid patients. The diabetic patients are indicated by crosses and the thyroid patients by dots, the straight line curve representing the general trend of the points is suggested as a method for predicting probable metabolism from measured insensible perspiration.

series of experiments dealt immediately not so much with the influence of environmental temperature as with the influence of the skin temperature at the time of noting the insensible perspiration. The results of these experiments showed that there was no material alteration in the metabolism or in the loss of weight of the men subjects, there being only a slightly greater loss of weight at the highest temperature (26 C) than at the lowest temperature (16 C). On the other hand, the preliminary cooling to which the women were subjected during the first hour and a half (at an environmental temperature of 16 C) was so great that in the subsequent periods of increased environmental temperature it was impossible to raise the skin temperature to approximate that which would normally be expected after a night's repose in bed, under bed

clothing Hence the insensible loss, as measured, was always much lower than would be expected from the curve in figure 3

When the loss in weight and the metabolism of members of the Nutrition Laboratory staff (i e., normal subjects) were simultaneously measured, it was found that in many instances their insensible perspiration was much lower in relation to their metabolism than would be expected from the curve given in figure 3 A survey of the skin temperature at six various points under the clothing and on the face and forehead showed that the skin temperature was cold By warming up the room and by covering the subject with more blankets, there was an increase in the loss of weight, accompanied by an increase in the skin temperature In the case of the normal women subjects it was noted that the scanty modern attire resulted in a cold skin temperature, particularly on the extremities Only when they were well protected with blankets and the skin temperature had attained that point which would be reached after a night's rest in bed, was the insensible loss at all comparable to that of the men subjects, who are usually much more warmly clad than are women An experiment was therefore made, designed to test out this particular point as to the influence of differences in protective clothing One of the women subjects was liberally wrapped in blankets, both under and over her, and long socks were drawn over the feet and legs By this means her skin temperature was made to approximate that which would obtain if she had been lying in bed, but care was taken to avoid overheating and the possibility of visible perspiration Under these conditions the insensible loss, when referred to the total metabolism simultaneously measured, was exactly that predicted by the slope of the line given in figure 3

In this connection it is interesting to point out that evidence has been furnished by Viale,⁵⁰ which indicates that, in accordance with a hypothesis of Galeotti, not only is the cutaneous circulation affected by a cold skin temperature but likewise the pulmonary circulation Thus, Viale finds that as a result of a cold skin temperature the temperature of the expired air falls perceptibly, which would of itself lower the amount of water brought out by the expired air

IDEAL CONDITIONS FOR MEASUREMENT

From a practical standpoint no one would think of measuring a hospital patient in a room at a temperature of 16 C or when the skin temperature was very low On the other hand, experiments made under conditions resulting in the appearance of visible perspiration are, at least until further experimental evidence is forthcoming, ruled out

⁵⁰ Viale, G. Rapporti tra la temperatura dell'aria espirata e la temperatura cutanea, *Arch per le sc Med* **43** 40, 1920, *Rapports entre la température de l'air expiré et la température cutanée*, *Arch ital de biol* **72** 32, 1923

At 26 C, for example, it is not unlikely that there may be visible perspiration, certainly with thyroid patients and with some normal subjects. It is believed, therefore, that the ideal conditions for the measurement of the insensible perspiration require that the subject should be lying, comfortably warm, either clothed and preferably covered with one or more thicknesses of blanket, or in bed with sufficient bedding to insure that the hands and feet are not cold and yet the subject does not feel so warm that visible perspiration is induced. Light moisture at the armpits probably does not affect the results. One should look for perspiration not only on the palms and face but also on the back, where contact with the bed may cause sweating. Under these conditions an environmental temperature of not far from 23 C will be found satisfactory. Measurements may undoubtedly be made at temperatures below 23 C, if the subject has more covering, but above 26 C (perhaps even with no blankets covering the subject) visible perspiration may be expected and should be looked for by the experimenter. Ordinary bed clothing will be all that is necessary for bedridden patients.

We are convinced that many of the deviations from the straight line curve exhibited in figure 3 may well be explained by the actual environmental temperature at which the experiments were made, or, more properly speaking, by the skin temperature, extremely low values for loss in weight unquestionably being explainable by low temperatures. It is realized that skin temperature measurements are not as yet possible in all clinics, although the apparatus is extremely simple and may be generally afforded.⁵¹ Means⁵² has shown that variations in the metabolic rate are accompanied by variations in the rate of blood flow. Thus, in muscular work and in hyperthyroidism the increase in rate of blood flow nearly parallels the increased metabolism. The loss of water vapor from the skin would seem to depend in part on the rate of blood flow under standard conditions of environmental temperature.

NORMAL CONTROL MEASUREMENTS

To control the accuracy of the suggested relationship between the loss in weight and the metabolism it is essential that both be measured at the same time or at essentially the same time. This requirement, however, immediately makes questionable the comparison of the loss overnight (determined on the silk scales) with the metabolism measured the next morning. Experiments in which the loss has been measured overnight on the silk scales and again the next morning on a more

51 Benedict, F. G., Miles, W. R., and Johnson, A. The Temperature of the Human Skin, *Proc. Nat. Acad. Sc.* 5 218 (June) 1919, Benedict, F. G. Die Temperatur der menschlichen Haut. *Asher-Spiro's Ergebn. d. Physiol.* 24 595, 1925 (Sold by W. C. Collins, 584 Huntington Ave., Boston).

52 Means, J. H. Circulatory Disturbances in Diseases of the Glands of Internal Secretion, *Endocrinology* 9 192 (May) 1925.

sensitive balance, with a simultaneous measurement of the metabolism, indicate that the factors affecting the loss overnight may have a compensating effect. Thus, the metabolism in the early evening is somewhat elevated due to the after-effects of the evening meal. Deep sleep results in a decreased metabolism, and the awakening in the morning again causes an increased metabolism. It is therefore probable that the metabolism measured after a weighing period in the morning closely approximates the average metabolism for the entire night, and it is believed that if the weights on the silk scales are carefully made, they are of equal value with those measured on delicate scales.

The control of the slope of the straight line curve in figure 3 with normal data is not simple, for although it is easy to secure members of the laboratory staff, i. e., normal persons, having a moderately low metabolism, persons having a basal heat production of 2,500 calories are not common. However, fourteen normal persons have been studied under the ideal conditions stipulated above and their measurements (essentially simultaneously determined) lie close to this line. Hence we feel justified in proposing, tentatively, a straight line curve of the order of that shown in figure 3 for use in comparing the *measured* insensible perspiration under the conditions stipulated with the *probable* metabolism at the time of measurement. With the accumulation of further data we are quite prepared to look for a slight change in the slope of this line. Indeed, our own experience with normal subjects has led us to believe that the inclination of the upper (broken) part of the line may perceptibly decrease. With at least one normal subject, whose hourly loss in weight was 50 Gm, the tendency has been for the plotted point indicating the relationship between the insensible perspiration and the measured metabolism to lie somewhat below the line, at about 2,400 calories. In this case, however, the metabolism is even higher than would be predicted by the curve. A possible explanation of this discrepancy between the normal data and the thyroid data at this upper part of the curve may be that with thyroid patients the proportion of water lost from the lungs and from the skin, which apparently is fairly regular up to 45 or 50 Gm, may be disturbed, due to the higher vascularity of their skin and that visible perspiration may be about to break out. The thyroid and the normal subject might have the same metabolism, and yet the skin of the thyroid patient might be hotter and more moist than that of the normal subject and thus more water would be given off from the skin. When the hourly loss in weight reaches about 50 Gm or over, therefore, the probabilities are that the predicted metabolism, based on the curve in figure 3, will be for normal individuals low rather than high.

In a direct comparison of the loss in weight and the metabolism it is important to emphasize that the subject should be more or less

accustomed to metabolism measurements, for with an apprehensive subject a psychic disturbance may occur which will result invariably in too high a metabolism (as a rule the measured metabolism is rarely, if ever, *below* basal) Indeed, it should be pointed out that the subjects studied in connection with the data plotted in figure 3 were not apprehensive They had become accustomed to having their metabolism measured frequently, in some cases daily Likewise, the patients were in all instances in the hospital on the night previous to the measurements and therefore had not undergone the excitement and exertion of a journey to the hospital without breakfast

PRACTICAL USE OF MEASUREMENT OF INSENSIBLE PERSPIRATION IN PREDICTING METABOLISM IN LABORATORY AND CLINIC

In the practical use of this curve the metabolism may be predicted from the insensible perspiration accurately measured either on a delicate balance during a period of from one to two hours or on the silk scales for a period of from nine to ten hours, the loss per hour being computed at the end of the period of measurement It is immaterial whether the subject is in a basal condition or whether the measurements are made after the ingestion of food, whether they are made during a moderate amount of regular exercise or, indeed, during fever We have every reason to believe that the loss as thus accurately measured predicts with reasonable correctness the metabolism *obtaining at the time the loss in weight was determined*, but not during any other period Thus, the loss when the subject is lying quietly, without food in the stomach and without fever, may not be referred to the metabolism after the subject has had food or has a febrile temperature

To use this chart, however, for the practical purpose of giving a clue as to the probable *basal* metabolism, it is obvious that the measurements of the loss in weight should be made not only under the conditions outlined above, but likewise under the conditions ordinarily required for basal metabolism measurements, that is, during complete rest and with the subject in the postabsorptive condition, or about twelve hours after the last meal To insist on the postabsorptive condition is practical when the measurements are made in the hospital on an accurate balance, which will permit measurements over a short period of time On the other hand, when the measurements are made overnight on the silk scales, it would be somewhat of a privation to submit the subject to a twelve hour fast prior to the evening weighing and then not allow him food until the next morning after the final measurements are made Under these conditions a light supper at 6 p. m., containing a minimum of ketose sugar such as levulose or sucrose, is permissible The insensible perspiration thus measured, when referred to the curve in figure 3, will

give a clue as to the probable basal metabolism. By likewise predicting the subject's basal metabolism from the normal standards based on the characteristics of the individual (age, sex, height, weight or surface area), one can note whether or not the metabolism as predicted from the insensible perspiration is higher or lower than that predicted for the average subject of like physical characteristics. Thus, if the subject has a loss in weight of 25 Gm per hour, determined when there is no food in the stomach and when there is no undue activity, he should have a basal heat production of not far from 1,250 calories for twenty-four hours. If the loss in weight is measured under basal conditions, it is proper to refer this heat production of 1,250 calories to the metabolism predicted from any of the standards commonly used, taking into consideration age, sex, height and weight (as is done by Harris and Benedict⁵³) or age, sex and surface area (as is done by Du Bois⁵⁴).

The error in the prediction of the metabolism from the insensible loss by this curve has not been calculated, for as yet the number of persons who have been measured with scrupulous care is very small. Certainly the error of prediction may not be computed for the individual points given in figure 3 for, as already stated, it is probable that with more careful attention to the control of the environmental temperature and other details, such as not washing the face and hands and not wetting the hair, many of these deviations would disappear. With the accumulation of further simultaneous measurements of metabolism and insensible loss, the material for the computation of the error of prediction will be at hand. On the basis of the data available at present it can only be stated that between the insensible perspiration (measured under the conditions outlined above) and the simultaneously measured metabolism there is a relationship and that this relationship is sufficiently close to permit the use of the insensible perspiration as a general index of the probable metabolism of a subject. It is obvious that this method of approximating basal metabolism can never replace the accurate, painstakingly recorded basal metabolism measurements under "standard" conditions. The weighings overnight are simple, however, and add but an insignificant expense to the hospital care of the patient, and the general trend of the curve in figure 3 is such that it is believed that it will be helpful in the preliminary assessment of the metabolic condition of many patients.

To simplify the use of this curve, the values for the probable metabolism as predicted from the hourly insensible perspiration at 2 Gm intervals from 14 to 58 Gm are given in table 4.

53 Harris, J. A., and Benedict, F. G. *A Biometric Study of Basal Metabolism in Man*, Carnegie Inst., Washington, Pub. no. 279, 1919.

54 Aub, J. C., and Du Bois, E. F. *The Basal Metabolism of Old Men*, Arch. Int. Med. **19** 831 (May) 1917.

A relationship seemingly as close as that found in these experiments between the insensible perspiration measured under carefully controlled, standardized and reproducible conditions and the metabolism existing at the time of measurement may have important bearing in the clinic. Indeed, as early as 1869 von Leyden made use of measurements of insensible perspiration in studying fever, and subsequently Schwenkenbecher and Inagaki, Isenschmid, Krehl, Nobel and Meyer also made clinical use of this measurement. These investigators, however, were chiefly concerned in the water balance, a phase of metabolism which has only too slowly been given serious attention but which today is interesting a large number of physicians.

The determination of the insensible perspiration has already been found clinically useful at the New England Deaconess Hospital, in giving an approximation of the metabolism under conditions of natural rest,

TABLE 4—*Twenty-Four Hour Heat Production of Human Beings Predicted from the Insensible Perspiration per Hour*

Insensible Perspiration Gm	Predicted Heat Calories	Insensible Perspiration Gm	Predicted Heat Calories
14	900	38	1,655
16	965	40	1,715
18	1,028	42	1,775
20	1,090	44	1,840
22	1,155	46	1,900
24	1,215	48	1,965
26	1,280	50	2,025
28	1,345	52	2,085
30	1,405	54	2,145
32	1,470	56	2,210
34	1,530	58	2,275
36	1,590		

undisturbed by the physical inconvenience of mask or mouthpiece or by the psychical stimulus of the "laboratory test." In the accumulation of the pathologic data plotted in figure 3 numerous opportunities occurred to study the relationship between the metabolism and the insensible loss when there were great changes in the metabolism in the same individual. Thus, in several cases of toxic goiter it was noted that both the insensible loss and the metabolism were very high prior to operation but that following operation both decreased and, indeed, in reasonably close proportion. It would appear, therefore, as if the insensible loss might be of significance in indicating the lowering of metabolism following a goiter operation.

The following cases are also cited as examples of the clinical value of the measurement of the insensible perspiration.

REPORT OF CASES

CASE 1 (no. 3700)—Mrs. B., aged 50, who weighed 57 Kg., with a height of 158 cm., had lost 14 Kg. in six months, in spite of an apparently normal caloric intake. She had extreme nervous symptoms and was referred to the hospital by

an excellent internist as having a possible case of hyperthyroidism. Nov 10, 1925, a basal metabolism determination, the first she had ever had, indicated that her twenty-four hour heat production was 1,732 calories, or 38 per cent above normal by the Harris-Benedict standard. November 15, her insensible perspiration at night, during nine hours in bed, was 327 Gm per hour. On the basis of our study of the relationship between metabolism and insensible perspiration it was believed that this measurement almost surely proved that this was not a case of true hyperthyroidism (or an elevated basal metabolism), but that the element of apprehension and psychic disturbance was responsible for the abnormally high metabolism. Fortunately it was possible to check the metabolism determinations on two other occasions. Thus, November 16, her basal twenty-four hour heat production was 1,424 calories (13.5 per cent above normal) and, November 17, it was 1,410 calories (12 per cent above normal). Dr F H Lahey examined the patient and considered that no hyperthyroidism was present. This patient was extremely nervous and it was difficult to measure the metabolism satisfactorily. The experience in her case illustrates what is believed to be true, namely, that a single determination of the insensible perspiration *carefully* made may be more useful clinically than a *single* measurement of the basal metabolism by the ordinary methods.

TABLE 5—*Measurements of Basal Metabolism and Insensible Perspiration in Case 2*

Date	Heat Produced per 24 Hours, Calories	Deviation from Harris Benedict Standard,* per Cent	Insensible Perspiration per Hour, Gm	Radial Pulse
December 23	1,626	+44		
December 24			38.6	100
December 26	1,522	+35	44.2	152
December 29	1,466	+31	35.3†	112
December 30	1,612	+47		

* Based on actual weight on day of metabolism experiment.

† Asleep in this test.

In a second instance the measurement of the insensible perspiration gave valuable support to the diagnosis of hyperthyroidism.

CASE 2—Mrs H, aged 72, whose weight was 52 Kg, with a height of 152 cm, entered the New England Deaconess Hospital for treatment of "eczema," which was supposed to have been brought on by the taking of potassium iodide (about 1 Gm per day) for fifteen months. Previous to taking the potassium iodide she had been nervous, had lost weight, and had had paroxysms of rapid heart action. The potassium iodide treatment had been followed by a gain in weight and improvement in heart action, but by little change in nervousness. On examination it was found that she had auricular fibrillation with an apex rate of 156, which was not affected by small doses of digitalis. She became nauseated after a few doses of digitalis by mouth and could not retain it by rectum. Direct examination showed very slight thyroid enlargement, slight eye signs, and tremor. Several measurements of both the basal metabolism and the insensible perspiration gave the results tabulated in table 5. Her extreme nervousness and discomfort while wearing the mask made interpretation of the high metabolism figures a little uncertain, especially in view of her age, the slight physical signs and her recent gain in weight. However, the constantly high insensible perspiration aided in making a diagnosis of hyperthyroidism, since it ruled out the possibility of the elevation in metabolism being due to nervousness, induced by the wearing of the mask and the sense of suffocation it produced in her.

The measurement of the insensible perspiration in a third instance gave information regarding the metabolism of a man too ill to wear any sort of face mask or mouthpiece

CASE 3 (no 169) —A man, aged 68, whose weight was 67 Kg, with a height of 170 cm, had had diabetes for eighteen years. Gangrene had necessitated the amputation of a leg two years previously. At the time in question he was admitted again to the New England Deaconess Hospital because of prostatic obstruction. He refused to continue a catheter existence and, in spite of the known risk, insisted on operation. Following a suprapubic cystostomy he became apathetic and mildly uremic, developed edema, and for weeks would eat nothing voluntarily. Intravenous injection of glucose, feeding by stomach tube, and rectal feeding were resorted to, until he resisted them all.

The striking feature of his case was the absence of ketosis, in spite of almost complete fasting. The amount of caloric intake is uncertain, because of vomiting. The food taken intravenously was the only food definitely to be estimated in the caloric intake, for even the food given per rectum was not always retained. However, for nine days his daily food intake had not exceeded 85 Gm of carbohydrate, 2 Gm of protein and 5 Gm of fat. It seemed likely that a low metabolism (in spite of a pulse rate around 90) might account for the absence of ketosis. His insensible perspiration was found to be 144 Gm per hour, an extremely small loss for a person of his weight, indicating a greatly depressed metabolism.

This case illustrates the value of the measurement of the insensible perspiration in making possible an approximation of the metabolism when, for practical reasons, the ordinary methods of determining the metabolism may not be employed.

SUMMARY

The significance of the loss in weight due to invisible, gaseous emanations, chiefly water vapor and carbon dioxide, or the so-called "perspiratio insensibilis," was recognized as early as 1614 by Sanctorius. Since that time measurements of this loss have occasionally been used in the clinic, chiefly as an aid in indicating variations in the water balance in the body.

In the research reported in this paper two methods were employed for studying the insensible perspiration. With platform scales, sensitive to 10 Gm, the insensible loss was determined overnight during a period of nine or ten hours, thus enabling the calculation of the hourly loss with an accuracy of approximately 5 per cent. An extremely sensitive balance, capable of weighing 100 Kg with an accuracy of 0.1 Gm, has also been used for measuring this loss in successive periods of from ten to fifteen minutes' duration. Measurements by these two methods indicate that in general the larger individual has the larger insensible perspiration.

Refinement in the method of measurement brought out sharply the influence of body size, ingestion of food and exercise on the insensible loss. Since these factors likewise affect the metabolism, it is evident

that there is a relationship between the insensible loss and the metabolism. Thyroid patients, whose metabolism is high, were found to have a large insensible loss, and diabetic patients, whose metabolism is low, were found to have a small loss. The relationship between the insensible perspiration and the metabolism of these two types of pathologic cases was such that when the data for the hourly insensible perspiration were plotted with reference to the twenty-four hour heat production, a straight line curve indicated the general trend of the metabolism.

The ideal conditions for measuring the insensible perspiration so that the data may be used for comparative purposes require that the body should be warm and comfortable, and that the extremities, particularly in the case of women, should be well protected. This fact was brought out when it was noted that the environmental temperature, which profoundly affects the skin temperature, plays a decided rôle in the insensible loss. When the insensible perspiration of either pathologic patients or normal subjects (workers in the laboratory) was measured under these ideal conditions and the metabolism was determined at essentially the same time, it was demonstrated that the straight line curve based on the data for diabetic and thyroid patients may serve as an excellent index of the metabolism obtaining at the time of measurement of the insensible perspiration, even with normal subjects.

Table 4 indicating the expected twenty-four hour heat production for insensible losses in weight of from 14 to 58 Gm per hour, at intervals of 2 Gm, shows that if the insensible loss is known, the probable metabolism can be readily approximated.

Practical use of this method in the clinic has already demonstrated its helpfulness.

THE RATE OF UREA EXCRETION AS A TEST OF RENAL FUNCTION BY MEANS OF A MODI- FICATION OF McLEAN'S INDEX *

SHOHEI KAWAHARA, M D

ROCHESTER, MINN

Although hitherto there have been several methods for testing renal function, few of them indicate accurately the ability of the kidney to excrete waste and metabolic end-products. The concentration and dilution tests are practical, and applicable for clinical purposes. It is possible to test the ability of the kidney to excrete foreign substances such as phenolsulphonphthalein, lactose, potassium iodide and indigo carmine, but no one test will give equally satisfactory information in all cases of renal insufficiency, and the result differs according to the type of case. In a study of the elimination of substances normally excreted by the kidney the estimation of nitrogen, urea, chlorides and so forth, following the ingestion of an analyzed or calculated diet must be considered. The micromethods of Ivar Bang, the system of blood analysis of Folin and Wu, and the investigations of V C Myers are valuable in the determination of the concentration of the metabolic products in the blood. In 1915, McLean ¹ introduced an index based on Ambard's law, which was designed to show the rate of urea excretion. At present the urea in blood and urine is estimated, the urine is measured, the body weight determined, and the index calculated from the following formula ²

$$\text{Index} = \frac{\text{Grams of urea for each twenty four hours gram } \sqrt{\text{urea for each liter of urine} \times 8.96}}{\text{Weight in kilos} \times (\text{grams of urea for each liter of blood})^2}$$

This test is especially convenient since it obviates the necessity of keeping the patient's diet constant. McLean ³ could take 10 cc of blood without injury to the patient, but the micromethod used in this study requires only 0.4 cc of blood. A short report is presented here of observations made on patients in the clinic.

* From the medical clinic of Prof. Dr. K. Miura, Imperial University of Tokyo.

1 McLean, F. C. The Numerical Laws Governing the Rate of Excretion of Urea and Chlorides in Man. I. An Index of Urea Excretion and the Normal Excretion of Urea and Chlorides, *J. Exper. Med.* **22** 212-236, 1915, II, The Influence of Pathological Conditions and of Drugs on Excretion, *ibid.* **22** 366-388, 1915.

2 McLean (Footnote 1, second reference).

3 McLean, F. C. Clinical Determinations of Renal Function by an Index of Urea Excretion. *J. A. M. A.* **66** 415-420 (Feb. 5) 1916, The Mechanism of Urea Retention in Nephritis. *J. Exper. Med.* **26** 181-199 (Aug.) 1917.

METHOD OF EXAMINATION

As a rule this procedure requires a period of seventy-two minutes, either during the forenoon or the afternoon, but not directly after a heavy meal. The subject must abstain from food and water during the period of the test. At the beginning of the period, the bladder is emptied. Thirty-six minutes after the test is completed blood is taken from a lobe of the ear and the urea in the whole blood is estimated by means of Bahlmann's⁴ micromethod. At the end of the period the bladder is again emptied, this specimen of urine, representing the total amount secreted during the test period is collected, carefully measured, and used for analysis. The urea in the urine is estimated by the same method as the urea in the blood. The rate of excretion is actually determined for the seventy-two minute period, and calculated for twenty-four hours as a standard period on which to base all the results. McLean had the subject drink from 150 to 200 cc of water half an hour before the test but I have usually not found this necessary in my work.

I have chosen Bahlmann's micromethod for the estimation of blood urea, and the test can be carried out daily, if necessary, without harm to the patient since it requires only 0.4 cc of blood. When there was great edema of the face the blood was taken from the arm vein, lest in taking blood from the lobe of the ear lymph should be mixed with the blood.

The urease, used for the estimation of urea, was prepared from the bean "Nata-mame" (*Canavalia gladiata*) according to Nagasawa's⁵ method.⁶

Yanagi⁷ modified the apparatus of Bahlmann's micromethod by inserting in the stopper a small funnel whereby the sodium carbonate can be poured into the main tube without danger of the escape of ammonia. When this modified apparatus was used the results were calculated with a slide rule.

INDEX OF PATIENTS WITH NORMAL RENAL FUNCTION

The index of urea excretion in normal persons may vary within wide limits

4 Bahlmann, R. Microdetermination of the Content of Urea in Blood by Means of Urease, *Nederl Tijdschr v Geneesk*, **1** 473-478 (Feb 7) 1920

5 Nagasawa, S. *Kyoto-Igaku-Zasshi* **17** 54

6 In 1920 Nagasawa reported that the radicle of the bean "Nata-mame" (*Canavalia gladiata*) contains an enormous quantity of urease, and he prepared a powerful urease from it. I have learned that the cotyledon of the bean also contains considerable urease, and have prepared urease from the cotyledon by the following method. After the beans have stood in water at room temperature for twenty-four hours, the skins of the beans are removed, the cotyledons crushed into small pieces, dried in a desiccator, and the residue dried once more. The powder thus obtained is urease.

7 Yanagi, K. New Colorimetric Method for Determination of Urea with Urease, *J A M A* **82** 1169-1171 (April 12) 1924

For the purpose of studying the limit of normality I have made some observations in a series of patients whose kidneys were found to be intact. The extremes of American authors usually lie between 80 and 200, in my observations of Japanese they are somewhat lower, fluctuating between 60 and 146 (table 1)

TABLE 1—Observations on Patients with Normal Renal Function

Case	Sex	Age Years	Diagnosis	Weight, Kg	Urine in Twenty- Four Hours, Cc	Urea			Index
						Gm for Each Liter of Blood	Gm for Each Liter of Urine	Gm for Each Twenty- Four Hours	
1	♂		Typhoid spine	46.45	1,170	0.21	5.40	6.32	66
2	♀	17	Epilepsy	44.2	1,360	0.52	16.87	22.94	70
3	♂	47	Hemiplegia dextra	48.4	1,900	0.30	10.78	20.48	146
4	♂	44	Carcinoma ventriculi	42.0	500	0.58	33.08	16.54	60
5	♂	27	Pleuritis exsudativa dextra	41.0	1,440	0.43	15.23	21.93	100
6	♂	23	Pleuritis exsudativa sinistra	41.0	600	0.35	18.90	11.34	88
7	♂	44	Amyotrophic lateral sclerosis	44.7	4,600	0.27	2.63	12.10	56
8	♀	25	Pleuritis exsudativa duplex	46.3	1,260	0.28	11.81	14.88	127
9	♀	58	Pachymeningitis cervicodorsalis and cataract	42.5	1,640	0.16	4.50	7.38	139
10	♀	21	Caries of the spine	43.6	1,960	0.37	9.99	19.58	92

* In this and the following tables, ♂ indicates male, ♀, female

INDEX OF PATIENTS WITH RENAL DISEASE

Albuminuria—The index was somewhat below normal in two patients whose urine showed only a faint trace of albumin (table 2)

TABLE 2—Patients with Albuminuria

Case	Sex	Age, Years	Diagnosis	Weight, kg	Urine in Twenty- Four Hours, Cc	Urea			Index
						Gm for Each Liter of Blood	Gm for Each Liter of Urine	Gm for Each Twenty- Four Hours	
1	♂	16	Icterus catarrhalis	38.6	860	0.27	6.67	5.75	47
2	♀	31	Amyotrophic lateral sclerosis	40.8	2,100	0.32	4.98	10.46	50

Acute and Chronic Nephritis—In a series of twenty-four cases of nephritis all the patients were in a serious condition except six (cases 1, 2, 3, 8, 14 and 15 table 3). Albumin was plentiful in the urine in the serious cases, and many blood cells, leukocytes, epithelial cells, hyaline and granular casts were to be found, there was hypertension of varying degree, and edema, which was marked and diffuse in certain cases. The index was low, varying from 1 to 35.

In cases 1, 2, 8, 14 and 15, in which the patients were convalescing from nephritis or were in an improved state with only a faint trace of albumin in the urine and no casts or other abnormalities, the index was

normal or nearly so. The phenolsulphonphthalein test in these cases showed that renal function was almost normal, for example, in case 1 the return was 73 per cent in two hours, and in case 2, 65 per cent. The patient in case 3 was also improving, but diuresis was extreme because of the effect of a diuretic (a decoction of *zea* 60 100 0), and the kidneys were in an irritable condition.

TABLE 3—*Patients with Acute and Chronic Nephritis*

Case	Sex	Age, Years	Diagnosis	Test	Weight, Kg	Urine in Twenty Four Hours, Cc	Urea			Index
							Gm for Each Liter of Blood	Gm for Each Liter of Urine	Gm for Each Twenty- Four Hours	
1	♂	26	Acute nephritis	1	54.75	3,600	0.15	2.00	7.20	74
2	♂	22	Chronic nephritis	1	54.6	700	0.26	8.75	6.13	44
3	♀	21	Acute nephritis	1	50.7	2,500	0.12	3.60	9.00	210
4	♀	18	Hemorrhagic nephritis, pleuritis exsudativa sinistra and peri- tonitis	1	40.0	780	0.34	8.10	6.32	35
5	♂	43	Sclerotic kidney and retinitis albuminurica	1	44.65	2,500	0.40	4.13	10.33	26
6	♂	43	Chronic nephritis	2	44.8	2,300	0.76	5.89	13.55	12
7	♂	43	Chronic nephritis	1	40.0	700	0.86	5.10	5.67	5
8	♂	43	Chronic nephritis	2	40.0	2,000	0.45	11.25	22.50	83
9	♂	16	Acute nephritis	1	36.2	520	0.53	3.65	1.89	3
10	♂		Diabetes mellitus and chronic nephritis	1	43.3	3,100	0.52	2.70	8.37	11
11	♂		Diabetes mellitus and chronic nephritis	2	44.65	2,480	0.60	1.50	3.72	3
12	♂		Diabetes mellitus and chronic nephritis	1	51.9	3,400	0.38	1.30	4.42	6
13	♂	20	Chronic nephritis	1	38.6	2,000	0.35	3.75	7.50	28
14	♂		Chronic nephritis	2	38.6	1,370	0.24	4.43	6.07	57
15	♂		Chronic nephritis	3	40.0	900	0.21	4.53	4.08	44
16	♂	55	Chronic nephritis and hemi- plegia dextra	1	50.4	2,000	0.37	3.75	7.50	19
17	♂	56	Chronic nephritis	1	66.55	500	1.10	10.80	5.40	2
18	♂		Chronic nephritis	2	68.40	540	0.96	12.15	6.56	3
19	♂		Chronic nephritis	3	68.75	330	0.80	16.63	6.34	5
20	♂		Chronic nephritis	4	69.20	600	1.14	16.43	9.86	4
21	♂		Chronic nephritis	5	71.20	600	0.89	13.43	8.06	5
22	♂		Chronic nephritis	6	70.5	400	1.33	17.25	6.90	2
23	♀	25	Sclerotic kidney	1	36.0	1,600	1.01	2.10	3.36	1
24	♀	25	Sclerotic kidney	2	36.0	1,900	1.12	6.08	11.55	4

Heart Failure—In the cases of heart failure the index was low in the state of severe decompensation (cases 1 and 2, table 4). When digitalis had increased the diuresis and caused the disappearance of the edema, the index was normal (case 3).

TABLE 4—*Patients with Heart Failure*

Case	Sex	Age, Years	Diagnosis	Weight, Kg	Urine in Twenty Four Hours, Cc	Urea			Index
						Gm for Each Liter of Blood	Gm for Each Liter of Urine	Gm for Each Twenty- Four Hours	
1	♀	67	Defect of aortic valve with cardiac asthma	41.0	3,500	0.67	2.70	9.45	8
2	♀	36	Defect of mitral valve	34.7	600	0.72	3.62	2.17	2
3	♀	36	Defect of mitral valve	45.0	3,700	0.34	5.40	20.30	100

Mediastinitis—In a case of mediastinitis in which the circulation was severely disturbed and the edema was marked and diffuse, I found a low index (table 5)

In the experience of Brugi⁸ the ureosecretory coefficient during general infection was almost constantly increased. This increase disappeared during convalescence. Aubertin and Rigal⁹ showed that a permanent hypertension may coexist with a normal secretion of urea, but I have not observed such cases.

TABLE 5—*A Patient with Mediastinitis*

Case	Sex	Age, Years	Weight, kg	Urine in Twenty Four Hours, Cc	Urea			Index
					Grams for Each Liter of Blood	Grams for Each Liter of Urine	Gm for Each Twenty Four Hours	
1	♂	44	62.0	2,400	0.88	13.73	33.00	22

SUMMARY

McLean's index is practicable as a test of renal function, although for repeated examinations its value is enhanced by the use of Bahlmann's micromethod for urea determination. The procedure is adaptable to clinical use since it is not necessary to keep the diet constant on account of it. If the index shows a normal value the protein in the diet need not be so rigidly restricted as otherwise.

⁸ Brugi, A. Ambard's Coefficient in Infections, Policlínico (sez. med.) **31** 366-372 (July) 1924.

⁹ Aubertin, C., and Rigal, E. Ureosecretory Coefficient in Hypertension, Bull. et mem. Soc. med. d. hôp. de Paris **48** 1167-1172 (July 18) 1924.

GASTRIC AND DUODENAL ULCER

FREQUENCY, NUMBER, SIZE, SHAPE, LOCATION, COLOR SEX
AND AGE IN SEVEN THOUSAND SEVEN HUNDRED
NECROPSY RECORDS AT BELLEVUE HOS-
PITAL, NEW YORK ¹

MILLS STURTEVANT, M D

AND

LOUIS L SHAPIRO, M D

NEW YORK

The frequency with which statistics of gastric and duodenal ulcer compiled forty or more years ago are quoted in modern systems of medicine and manuals of diseases of the stomach has led us to search the Bellevue Hospital necropsy records from 1904 to 1922 with the purpose of finding out if such figures show any change. A portion of this study is reported here and compared with other published figures, surgical and postmortem. Welch's figures in Pepper's System of Medicine published in 1885, Berthold's statistics in 1882, Leube's tables in Ziemssen's Cyclopaedia of 1876, Brinton's figures in his book of 1859 and Lebert's book of 1878 are all examples of statistics covering periods ending more than forty years ago, still doing duty.

While necropsy statistics are open to certain objections ¹ in determining the frequency of gastric and duodenal ulcer, they probably afford the best means obtainable ². Small scars or ulcers may be impossible of detection or may be overlooked, just as a small ulcer is sometimes difficult or impossible to find at operation ³. Acute ulcers may leave no scars. A large number of necropsies represents the dead of a charity hospital serving the poor of a large city. Such a group may not represent properly the country, the state, or even the entire city. Medical diagnoses on living subjects, even roentgen-ray diagnoses, must contain a greater percentage of error, while surgical records include only such patients as through the advice of their physicians or from their own initiative seek surgical aid.

The patients of Bellevue Hospital are of all ages. The necropsies are all those permitted on patients who have died in the hospital or

* From the gastro-enterologic clinic of the University and Bellevue Hospital Medical College

1 Riegel, Franz. Encyclopedia of Practical Medicine, Disease of the Stomach, 1905, p. 548.

2 Fenwick, Samuel, and Fenwick, W. S. Ulcer of the Stomach and Duodenum, Philadelphia, P. Blakiston's Son & Co., 1900, p. 78.

3 Sherren, James. Lectures on the Surgery of the Stomach and Duodenum, New York, Paul B. Hoeber, 1922, pp. 18-19.

those performed by the coroner or medical examiner Bellevue Hospital comprises the following services, gynecology, obstetrics, tuberculosis, psychopathic and nervous diseases, eye, ear, nose and throat, genito-urinary diseases, contagious diseases, baby and children's diseases, erysipelas, alcohol, prison, general medical, and general surgical

GASTRIC AND DUODENAL ULCER FREQUENCY

In 7 700 necropsy records, 120 cases of gastric ulcer were found, of which thirty-four were healed In the same 7,700 records, forty-four duodenal ulcers were found, of which nine were healed In five of these cases, the gastric and duodenal ulcers were found together, making a total of 159 cases in which either gastric or duodenal ulcers were found, or both

There were eighty-six cases of unhealed gastric ulcers, either single or multiple There were thirty-five cases of open duodenal ulcer, single or multiple The eighty-six cases of open gastric ulcer included four

TABLE 1—*Healed and Unhealed Gastric and Duodenal Ulcers in Seven Thousand Seven Hundred Necropsies*

	Number of Cases	Percentage in 7,700 Necropsies
Healed and unhealed gastric ulcers	120	1 558
Unhealed gastric ulcers	86	1 116
Healed gastric ulcers	34	0 441
Healed and unhealed duodenal ulcers	44	0 571
Unhealed duodenal ulcers	35	0 454
Healed duodenal ulcers	9	0 116
Healed and unhealed gastric and duodenal ulcers	159	2 064
Unhealed gastric and duodenal ulcers	117	1 519
Healed gastric and duodenal ulcers	48	0 568

cases with open duodenal ulcers These were also counted in the thirty-five cases of open duodenal ulcer, so there were 117 cases of unhealed gastric or duodenal ulcer or both One patient with open gastric ulcer also had a healed duodenal ulcer

So in 7,700 necropsy records of the very active service at Bellevue Hospital about 2 per cent had either gastric or duodenal ulcer or had evidence of having had an ulcer These are somewhat near Berthold's ⁴ figures of 2 7 per cent, but far from Grunfeld's ⁵ figures of 20 per cent of necropsies Bassler ⁶ compiled 59,450 necropsy records from various sources, the authorities not being given, and states that 4 4 per cent showed open or healed gastric or duodenal ulcers A series of

⁴ Berthold A H F Statistischer Beitrag zur Kenntnis des chronischen Magengeschwurs, Sections-Protocoll d Path Inst Berlin, 1883, pp 7-8

⁵ Grunfeld Frederick Nagle Bemaerkninger om Cikatricer efter Ulcus Ventriculi und Ulcus Duodeni, Hosp Tid 60 765, 1882

⁶ Bassler, Anthony Diseases of the Stomach and Upper Alimentary Tract, Philadelphia F A Davis Company, 1922 p 562

8,534 necropsies from the Eppendorf Institute at Hamburg showed about 1.5 per cent of ulcers.⁷

Our figure of 1.5 per cent gastric ulcers is lower than most of the published statistics. Leube⁸ in 13,605 necropsies found 653, not quite 5 per cent. Fenwick² compiled 47,912 necropsies from various reports, largely Continental, and found 4.2 per cent gastric ulcers. Von Jaksch⁹ found 4.8 per cent, Brinton¹⁰ estimated 5 per cent. Welch¹¹ in a study of 32,052 necropsies, mainly Continental, also estimated 5 per cent. However, in 800 Bellevue Hospital necropsies he found only six ulcers. The following figures all based on necropsy study show the variation of European statistics. Nolte,¹² 1.23 per cent, Stahl,¹³ 2.16 per cent, Ziemssen,¹⁴ 4.55 per cent, Griess,¹⁵ 8.3 per cent, Riegel,¹⁶ 10 per cent. The lowest figure found is that of Lebert,¹⁷ one in 200. Lockwood¹⁷ found six in 1,000 necropsies at Bellevue Hospital. He quotes Harlow Brooks' nine in another thousand of Bellevue Hospital necropsies. Lockwood has compiled the figures of 19,315 necropsies in America, including Campbell Howard's¹⁸ figures, and found 238 gastric ulcers, or 1.23 per cent. Among the first thousand necropsies at Johns Hopkins Hospital there were nine gastric ulcers.¹⁹

The rarity of gastric ulcer in America as compared with Europe has been spoken of by Da Costa,²⁰ Welch,¹¹ Howard,¹⁸ Bolton²¹ and others.

About 1.12 per cent of our necropsies showed open gastric ulcers. Fenwick's² compiled series of 20,317 necropsies showed 1.37 per cent. Hemmeter's²² figure is 1.4 per cent of 11,888 necropsies, while Leube⁸ found 2.33 per cent.

7 Dietrich, Hans A. Statistische und etiologische Bemerkungen zum Ulcus pepticum duodeni, München med Wchnschr 59 638-640 (March) 1912

8 Leube W, cited by H. von Ziemssen in Cyclopaedia of the Practice of Medicine Ulcer of the Stomach, p 195

9 Von Jaksch, quoted by Bamberger, H, in Handb d spec Path u Therap, Virchow 6 280, 1855

10 Brinton William Diseases of the Stomach, 1859, p 133

11 Welch, W H Pepper's System of Medicine, 1885, p 480

12 Nolte, quoted by Hemmeter Häufigkeit des Magengeschwurs in München, Inaugural Dissertation, 1883, p 472 Hemmeter, J C Diseases of the Stomach, Philadelphia, P Blakiston's Son & Co, 1897, p 495

13 Stahl, quoted by Dreschfeld, Julius A System of Medicine, Allbutt and Rollston 1907, 3 443

14 Ziemssen, H Ueber die Behandlung des Magengeschwurs, Samml klin Vortr, 1871, pp 75-104

15 Griess, quoted by Hemmeter (Footnote 12, p 496)

16 Lebert, Hermann Die Krankheiten des Magens, 1878, p 180

17 Lockwood, G R Diseases of the Stomach, Philadelphia, Lea & Febiger, 1913, p 91

18 Howard, C P The Incidence of Gastric Ulcer in America, Med News 85 673-675 (Oct 8) 1904

19 Dreschfeld (Footnote 13)

20 Da Costa, J M Textbook of Medical Diagnosis, 1881, p 493

21 Bolton, Charles Ulcer of the Stomach, 1913, p 24

22 Hemmeter (Footnote 12)

Nearly 21 per cent of our ulcers were healed and the proportion of healed to unhealed is very nearly 1 2 5 Leube found the almost equal figures of 278 open ulcers to 265 scars, while Hemmeter's figures were 164 unhealed to 373 healed

COEXISTENT GASTRIC AND DUODENAL ULCERS

Five patients out of 159 had both gastric and duodenal ulcers This is just over 3 per cent Double ulcer is found in over 16 per cent of the Mayos' cases²³ Perry and Shaw²⁴ in a series of 120 duodenal ulcers found fifteen cases of concomitant ulcers of the stomach This is 12 5 per cent, which is not far from our own series of forty-four duodenal ulcers that had coexistent stomach ulcers in 11 per cent On the other hand, our 120 gastric ulcers had duodenal ulcers in only 4 per cent

FREQUENCY OF DUODENAL ULCERS

In our series of nearly 8,000 necropsies records of forty-four duodenal ulcers, either open or healed, were found Nine of these patients had healed ulcers and thirty-five unhealed Cooley²⁵ has compiled 38,106 necropsies, 17,652 taken from Perry and Shaw and about 25,000 from German statistics, among which there were 158 duodenal ulcers or scars, 0 41 per cent Fenwick² found 0 26 per cent of 13,055 necropsies

About 20 per cent of our duodenal ulcers were healed Brinton¹⁰ in twenty-five ulcers found thirteen healed and twelve open In Perry and Shaw's²⁴ cases 11 per cent were healed

Of 159 healed and unhealed gastric and duodenal ulcers, four patients had both open gastric and open duodenal ulcers There was one case of open gastric and healed duodenal ulcer The proportion of gastric to duodenal ulcers was 2 72 1 Only 25 per cent as many patients with gastric ulcers apply to William Mayo for operation as patients with duodenal ulcers, Robson²⁶ gives 4 3, Einhorn,²⁷ 4 1, Reed,²⁸ 12 1

NUMBER OF GASTRIC ULCERS

Of 120 gastric ulcers eighty-six were single, and of the eighty-six single fifty-six were unhealed Of our stomach ulcers 71 66 per cent were single A series of 112 cases from the London Hospital² showed

23 Judd E S, and Proctor, O S Multiple Gastric Ulcers, *M J & Rec* **121** 93-95 (Jan 21) 1925

24 Perry E C and Shaw, L E On Diseases of the Duodenum, *Guy's Hosp Rep* **50** 171-308, 1893

25 Cooley, E B Duodenal Ulcer, *Illinois M J* **23** 187-193 (Feb) 1913

26 Robson, M A W, and Moynihan, B G A Diseases of the Stomach and Their Surgical Treatment, 1901, p 93

27 Einhorn, Max Diseases of the Stomach, 1900, p 222

28 Reed, Boardman Lectures to General Practitioners on the Diseases of the Stomach and Intestines, 1904, p 559

71.43 per cent single. Brinton found 79 per cent single, Leube, 80 per cent, and 80 per cent has been given by other investigators.

The largest number of ulcers counted in any one case was twelve. In five cases the number was given as "numerous" or "multiple." Berthold⁴ has described a case of thirty-four gastric ulcers and Lange²⁹ described a much quoted case in which the ulcers were so numerous as to make it impossible to count them. Affleck,³⁰ Robertet,³¹ Welti,³² Gaillard³³ and many others have described cases with many ulcers. Bolton²¹ mentions two cases of his, one with 431 ulcers and one with 250.

TABLE 2—*Number of Ulcers in a Single Case, Healed and Unhealed*

		Percentage in 7,700 Necropsies	Percentage in 120 Cases
Single ulcers	86	1.116	71.66
Two ulcers	14	0.181	11.66
Three ulcers	7	0.090	5.83
Four ulcers	2	0.025	1.66
Five ulcers	3	0.038	2.50
Six ulcers	1	0.012	0.83
Eight ulcers	1	0.012	0.83
Twelve ulcers	1	0.012	0.83
Multiple ulcers	5	0.064	4.16
Single ulcers	86	1.116	71.66
Two or more ulcers	34	0.441	28.33

TABLE 3—*Number of Healed and Unhealed Ulcers in Different Groups in Table 2*

Single Ulcers	Open	Open, per Cent	Healed	Healed, per Cent
86	56	65.11	30	34.89
Number of Ulcers	All Open	One Healed	Two Healed	Three Healed
Two	9	3	2	
Three	5			2
Four	2			
Five	2	1		

Of 120 gastric ulcers twenty-one were acute, or 17.5 per cent. Figured in proportion to the eighty-six that were open, twenty-one are 24.4 per cent. Fenwick gives 29 per cent of 112 cases as acute. Of our acute ulcers eleven were multiple and ten single, which corresponds with Carless'³⁴ figure of 50 per cent multiple.

Leaving our acute ulcers out of the foregoing estimate we have ninety-nine chronic ulcers and scars. Of these twenty-three, or nearly 23 per cent, were multiple.

29 Lange. Deutsch Klinik **12** 9 (March 3) 1860, *ibid* **12** 10 (March 10) 1860.

30 Affleck, J. O. Tr. Edinburgh Med.-Chir. Soc., Lancet **1** 478, 1901.

31 Robertet. Bull. Soc. anat. de Paris **8** 499-502 (Nov.) 1863.

32 Welti, Emil. Centralbl. f. allg. Pathol. u. path. Anat. **1** 537 (Aug. 5) 1890.

33 Gaillard, M. L. Bull. et mém. Soc. méd. d'Hôp. de Paris **9** 809 (Nov. 18) 1892.

34 Carless, quoted by Osler, William, and McCrae, Thomas. Modern Medicine **5** 185, 1908.

In each of the remaining cases of multiple ulcers all the ulcers were unhealed

NUMBER OF DUODENAL ULCERS

Of the twenty-four single ulcers five were healed, leaving nineteen single open duodenal ulcers. This is 43.18 per cent of all duodenal ulcers healed and unhealed and 54.28 per cent of the open duodenal ulcer cases. One of the five patients with single duodenal ulcer scar had an open gastric ulcer. Of the twelve patients having two ulcers, one had both healed, one had one healed. In the case with three ulcers, all three were healed. In one of the cases with five ulcers all five were healed. Of the nineteen patients with single open ulcer, two had open gastric ulcers. Of the ten patients with two open ulcers, one had an open gastric ulcer. The patient with one open ulcer and one scar also had an open gastric ulcer.

In each of the remaining cases of multiple duodenal ulcer all the ulcers were unhealed. One hundred and sixty duodenal ulcers compiled from the literature²⁴ gave fourteen cases in which two ulcers were present and nine cases in which there were more than two, or

TABLE 4—*Number of Ulcers in a Single Case, Healed and Unhealed*

		Percentage in 7,700 Necropsies	Percentage in 44 Cases
Single ulcers	24	0.311	54.54
Two ulcers	12	0.155	27.28
Three ulcers	1	0.012	2.27
Four ulcers	1	0.012	2.27
Five ulcers	2	0.025	4.54
Six ulcers	2	0.025	4.54
Twenty-five ulcers	1	0.012	2.27
Multiple ulcers	1	0.012	2.27
Single ulcers	28	0.311	54.54
Two or more ulcers	20	0.259	45.45

14.3 per cent multiple as compared with our 45 per cent. Morat's³⁵ figures gave 82 per cent single. Sippy³⁶ stated that more than 20 per cent of duodenal ulcer patients have two or more ulcers. In one of our cases twenty-five ulcers were noted and in another they were described as numerous.

SIZE OF GASTRIC ULCER

Of eighty-six cases of open gastric ulcer five were in infants. These were all acute ulcers. One patient had two ulcers, each 4 mm in diameter. One patient had three ulcers described as minute. Three patients had one ulcer each, in two instances described as small and in one case the size not being given.

³⁵ Morot Pierre. *Essai sur l'ulcère simple du duodenum* (Paris: Imprimeur de la faculté de médecine, 1865).

³⁶ Sippy B. W. *Nelson Loose-Leaf Medicine* 5:240.

Of the eighty-one cases remaining, there were fifty-three cases of single ulcer. In three of these the size was not given. One case was described as large. In thirty-seven cases one dimension was given and in twelve cases two dimensions were given. Table 5 gives the dimensions in these forty-nine single ulcers.

TABLE 5—*One or Two Dimensions in Forty-Nine Cases of Single Gastric Ulcer*

Number of Cases	First Dimension, Cm	Second Dimension, Cm
2	0.5	
2	1.0	
2	1.25	
4	1.5	
4	1.75	
5	2.0	
5	2.5	
1	3.0	
2	4.0	
3	5.0	
1	7.0	
1	0.8	0.4
1	0.5	0.2
1	1.0	1.5
1	1.0	2.0
2	1.5	2.0
1	1.25	2.5
1	2.5	3.0
1	1.0	3.0
1	2.0	3.5
1	3.5	5.0
1	5.0	6.0

There were twelve cases with two ulcers, both open. The size was given in eight of these. Table 6 gives the size of one or both ulcers in the eight cases with two open ulcers.

TABLE 6—*Dimensions in Eight Cases of Two Open Gastric Ulcers*

Number of Cases	First Ulcer, Cm	Second Ulcer, Cm
1	0.5	0.5
1	1.0 by 0.8	Not given
1	1.75	Not given
1	2.5	1.25
1	3.5 by 2.0	1.5
1	4.0 by 1.5	0.4
1	4.0 by 5.0	Not given
1	5.0 by 6.0	2.0

There were five cases with three open ulcers. In one of these the size was not given for any of the ulcers. One was given as from 0.2 to 0.7 cm for the three ulcers. In one case the size of two of the ulcers was not given while the third was given as 1.5 by 0.5 cm. In the fourth case the size of one ulcer was not given, the other two were measured as 0.4 and 0.75 cm in diameter, respectively. In the last case the size of two of the ulcers is given as less than 1, while the third ulcer was 2 cm in diameter.

There were two patients with four open ulcers each. In one of these cases the largest ulcer was 1.5 cm in diameter, the remainder

were less than 0.5 cm in diameter. In the other case the ulcers were each less than 0.5 cm in diameter.

There were three patients with five ulcers each. In one case one of the ulcers was healed. The remaining ulcers were not measured, but in the other two cases all the ulcers were less than 1 cm in diameter. In one case with six open ulcers all were less than 0.5 cm in diameter. One patient had eight open ulcers, all less than 1 cm in diameter.

In the cases described as numerous or multiple one ulcer was 4 by 1 cm. The remainder, such as were given, were all less than 1 cm.

Gastric ulcers may be so small as to be found with great difficulty,³ or so large as to involve the whole surface of the stomach,³⁷ or any size between these two extremes. Dreschfeld in Albutt's System of Medicine gives the size as generally less than 2.5 cm but quotes cases in which the ulcers were 6½ by 3½ inches (16.5 by 8.8 cm) and 6 by 3 inches (15.2 by 7.6 cm). Ewald says the size commonly runs from that of a five cent piece to a quarter, which is roughly from 2 to 2.5 cm. Among our forty-nine single ulcers measured the size ranged from less than 0.5 cm to 5 by 6 cm. The average of the longer measurement given for each ulcer is 2.35. In eight cases with two ulcers, the larger ulcers had the same range as the single ulcers, from 0.5 to 5 by 6 cm. The largest measurement in cases with three ulcers is 2 cm, in cases with four ulcers, 1.5 cm, in cases with five ulcers, less than 1 cm. In one case with six ulcers the largest measurement was less than 0.5 cm. Roughly, the ulcers may be said to be smaller as they increase in number in a single case. An exception to this is the ulcer 4 by 1 cm in a case described as multiple.

SIZE OF DUODENAL ULCERS

Of nineteen open, single duodenal ulcers, the size was given in fourteen. In two cases the ulcers were less than 1 cm in diameter. Eight had both diameters less than 2 cm and more than 1 cm. In two the measurements were between 2 and 3 cm. In one the ulcer entirely encircled the intestines. In one the ulcer was described as small.

Of ten cases having two open duodenal ulcers the size was given in seven. In two of these the diameter was 1 cm in one ulcer and 1 or less in the other, in three cases both ulcers measured between 1 and 2 cm, in one case one ulcer was 2 cm in diameter while the other was 2 by 1 cm, in the seventh case one ulcer was 2 by 0.5 cm, the other 0.4 cm in diameter.

In one case of four ulcers one ulcer was 2.5 cm in diameter, the others were all less than 1 cm. One patient with five ulcers had one less than 1 cm in diameter. In two cases of six ulcers the sizes were

³⁷ Dreschfeld (Footnote 13) p. 450

not given in either case. One patient had twenty-five ulcers. These were described as running from 2 mm to 2 cm. In one case with numerous ulcers the size was not given. The duodenal ulcers, except for one that entirely encircled the intestine, ranged from less than 1 cm to 2 cm in diameter.

SHAPE OF GASTRIC ULCER

Of eighty-six open gastric ulcers, the shape was given in seventy-eight. Of these fifty were given as round, rounded or circular. This included two cases of three ulcers, all rounded, one case of numerous ulcers, all rounded, and one case of two ulcers, both round. Eighteen cases were described as oval, all single ulcers. Seven cases were irregular. One case had two ulcers, both irregular. Two cases had encircling bands. One ulcer was kidney shaped.

Gastric ulcers are usually round or oval in outline,² from which characteristic they are often called round ulcer of the stomach. The authors have been able to find ulcers of the following described: round, oval, irregular, irregularly rounded, triangular, quadrilateral, band shaped, annular, serpiginous, linear, oblong, horseshoe, kidney shaped and starshaped.

SHAPE OF DUODENAL ULCERS

Of thirty-two open duodenal ulcers the shape of twenty-nine was described. Twenty-one were called circular, four were oval, two, irregular, and two band shaped. Duodenal ulcers are almost always oval or rounded. Occasionally they are quadrilateral or annular.

LOCATION OF GASTRIC ULCERS

Table 7 gives the location of the gastric ulcers as far as their location was described.

The relation to the cardia and pylorus is given in 129 ulcers. Fifty-five are at or near the pylorus, ninety-eight are within 8 cm of the pylorus, eight are at or near the cardia, fifteen are within 8 cm of the cardia, sixteen are in the midzone between the cardia and the pylorus, nine ulcers are on the anterior surface while twenty-seven are on the posterior surface, forty-one are on the lesser curvature, and nineteen on the greater curvature. The percentage is roughly 76 per cent near the pylorus, 12 per cent near the cardia, and 12 per cent in the midgastric zone.

Of the cases at the Mayo Clinic 90 per cent are in the pyloric end of the stomach. A series published by Charles Mayo in 1921 was: lesser curvature, 534, posterior wall, eighty-five, greater curvature, nine, anterior wall, five, and unrecorded, five. Eusterman's³⁸ figures

³⁸ Eusterman, G. B. The Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcers, *J. A. M. A.* 65:18 (Oct. 30) 1915.

from the same clinic in 1915 for 264 cases were lesser curvature, 63 per cent, pylorus, 13 per cent, at or near the pylorus, 33 per cent, posterior wall, 10 per cent, and anterior wall, 2 per cent. In neither of these series are any ulcers mentioned as being near the cardia. Sippy³⁶ compiled more than 3,000 necropsies, source not given, as follows: lesser curvature, 34 per cent, posterior wall, 30 per cent, pylorus, 12 per cent, anterior wall, 9 per cent, cardia, 6.5 per cent, fundus, 3 per cent, greater curvature, 3.5 per cent, and anterior and posterior wall, 1 per cent. This series gives but a single locating point for each ulcer. A certain number of the 30 per cent on the posterior wall were also probably near the pylorus, yet only those actually in the pylorus are mentioned in this relation. Welch's figures in *Pepper's System of Medicine* in 1885 and Fenwick's figures in his monograph of 1900 are similar to Sippy's and open to the same criticism.

LOCATION OF DUODENAL ULCERS

The location of forty-seven ulcers was given. Thirty-nine of these were in the first portion of the duodenum. Of this thirty-nine, two extended so as to involve the second portion, the eight remaining were in the second portion. There was no case with one ulcer in the second portion of the duodenum in which there was not one or more ulcers in the first portion.

COLOR AND SEX

Among 7,700 necropsy records searched, 120 gastric ulcers were found, healed and unhealed. Of these 120, 118 were in white persons and two in colored. Eighty-nine patients were male and thirty-one female.

Forty-four records of duodenal ulcers were found. All were in white persons. Of these thirty-four were males and ten females.

The rarity of gastric and duodenal ulcer in negroes has been noted by Wallace Frank and Louis Frank³⁹ and by Boulware. Apparently, it is rare in the South and rarer still among the colored.

The Fenwicks compiled 2,031 cases of open ulcer and found the proportion three females to two males. They do not say if their records are from postmortem or clinical records. Lebert⁴⁰ in 209 clinical cases found three and one-half females to one male. Rokitsanski⁴⁰ found forty-six female to thirty-three male, while Habershon found 127 women to seventy-four men. Surgical figures give the preponderance very definitely to men. Grouping gastric and duodenal ulcers William J. Mayo⁴¹ finds but little over 25 per cent in women. Necropsy figures

39 Frank, L. W. Duodenal Ulcer in a Negro, Case Report and Discussion, *Kentucky M. J.* 20:74 (Jan.) 1922.

40 Rokitsanski, Carl. *Med. Jahrb. des k. k. österr. Staates*, 1839, p. 184.

41 Mayo, W. J. Progress in Handling Chronic Peptic Ulcer. *Collected Papers of the Mayo Clinic*, 1922, p. 43.

TABLE 7—Location of Gastric Ulcers in One Hundred and Twenty Cases Found at Necropsy

[illegible]

give about even figures for the most part, Berthold,⁴ 128 men to 134 women, Grunfeld,⁵ 241 women to 209 men. From our figures we can only say that of the patients dying in Bellevue Hospital for the last twenty years, about three males have gastric ulcer to one female.

The figures for duodenal ulcer show considerable variation in the sex percentage involved. Perry and Shaw²⁴ found three men to one woman, Mayo (1905), seventy-seven to twenty-three, and Smith⁴² in a series of 113 ulcers had ninety-seven cases in males.

Our figures taken from necropsies are almost the same as those of Perry and Shaw similarly taken.

AGE IN GASTRIC ULCER

The age at death of patients in whom gastric and duodenal ulcer is found at necropsy is of little value in determining the age of onset of gastric and duodenal ulcer. Tables 8, 9, 10 and 11, however, are of interest in showing that ulcer may occur at all ages, that from the age of 30 to 50 figures are about the same, that they are doubled from the age of 50 to 60, and that this rate is pretty well maintained from 60 to 69. Obendorfer's⁴³ table is similar. His group from the age of 20 to 29 is larger proportionately and he has more cases from 70 on. The tables further show that of the kind of persons that go to necropsy at Bellevue Hospital there is an increasing proportion of gastric ulcers found in each ten year group of those dying, up to 70 years at the time of death. Leaving out the cases with scars does not increase the proportion of younger persons in whom ulcer was found at necropsy. That is, there are as many scars in the younger groups as in the older. In the third table the group from the age of 50 to 70 is 46 per cent, while in the first table this group is 52 per cent. Reed²⁸ says it is a disease of the middle period of life, belonging to the young more than to the old. Our figures fall short of his estimate that three fourths of the patients are between 20 and 60, though well over three fourths of our patients are between 30 and 70. Bassler's "third decade of life" is certainly denied by the numbers of ulcers we have found in advanced life. Many authors make a distinction in the ages of the sexes. Kemp⁴⁴ gives 20 to 48 in females, 40 to 50 in males, Abram's edition of Herschell's Textbook of Indigestion gives the average age of females as 27, of males as 36.7, Joslin gives 27 in females, 37 in males, Habershon,⁴⁵ from 20 to 50 in males, from 25 to 30 in females. Our table of ages by sexes fits in somewhat with this idea. The youngest

42 Smith, F. J. Gastric and Duodenal Ulcer, Brit. M. J. 1 673 (March 19) 1910.

43 Obendorfer. Ueber die Häufigkeit des Ulcus rotundum ventriculi in München, München med. Wchnschr. 56 1640, 1909.

44 Kemp, R. C. Diseases of the Stomach, Intestines and Pancreas, Ed. 2, 1912, p. 252.

45 Habershon, S. H. Diseases of the Stomach, 1909, p. 378.

woman in the series was between 30 and 40, and there were two in this group. The largest group is from 40 to 50 with five. The 50 to 60 group has nearly as many, while there are as many cases in the 60 to 70 and the 70 to 80 as there are in the 30 to 40. However much it may be a disease of young women it certainly may be present at any age. The men ran older, with the largest group from 60 to 70.

TABLE 8—*Age at Death of 117 Patients with Gastric Ulcers, Both Open and Healed, Compared with Age at Death in 7,219 Necropsy Records in Which Age Is Given*

	Number of Cases of Ulcer	Percentage of 117 Cases	Number in Each Group, of 7,219 Cases	Ulcers in Each Group, per Cent
Under 1 year	5	4.273 }	1,519	0.32
1-9	0			
10-19	1			
20-29	5	0.854	209	0.47
30-39	17	4.273	731	0.68
40-49	19	14.529	1,167	1.45
50-59	34	16.239	1,303	1.45
60-69	27	29.059	1,169	2.9
70-79	8	23.076	760	3.5
80-89	1	6.837	300	2.7
90-99	0	0.854	57	1.7
			4	

TABLE 9—*Age at Death in Three Hundred and Four Cases Given by Obendorfer*

Age	Number of Cases	Age	Number of Cases
10-19	5	50-59	49
20-29	21	60-69	55
30-39	24	70-79	33
40-49	41	80-89	11

TABLE 10—*Age at Death of Eighty-Four Patients in Whom Open Gastric Ulcers Were Found at Necropsy*

Age	Number of Cases	Percentage of 70 Cases Over 1 Year
Under 1 year	5	
1-9	0	
10-19	1	1.19
20-29	3	3.57
30-39	15	17.85
40-49	13	15.47
50-59	20	23.80
60-69	20	23.80
70-79	7	8.33

TABLE 11—*Ages at Death of Fifteen Females and Sixty-Four Males with Open Gastric Ulcers*

Age	Females	Males
10-19	0	1
20-29	0	3
30-39	2	13
40-49	5	8
50-59	4	16
60-69	2	18
70-79	2	5

AGE IN DUODENAL ULCERS

Fifty-nine per cent of our patients with duodenal ulcer were between the age of 40 and 70, and 10 per cent were between 70 and 80 In the

TABLE 12—*Age at Death of Forty-One Patients with Duodenal Ulcers, Open and Healed, Compared with Age at Death of Number of Whole Necropsy Series in Each Age Group*

Age	Number of Cases of Ulcer	Percentage of 41 Cases	Number of Cases in Each Group of 7,219 Cases	Percentage of Ulcers in Each Group
Under 1 year	1	2.43	1,519	0.13
1-9	1	2.43		
10-19	1	2.43	209	0.47
20-29	6	14.63	731	0.82
30-39	2	4.87	1,167	0.17
40-49	9	21.95	1,303	0.69
50-59	9	21.95	1,169	0.76
60-69	7	17.07	760	0.92
70-79	4	9.75	300	1.33
80-89	1	2.43	57	1.75
90-99	0		4	

TABLE 13—*Age at Death of Thirty-Two Patients in Whom Open Duodenal Ulcers Were Found at Necropsy*

Age	Cases	Per Cent
1-9	1	3.12
10-19	1	3.12
20-29	5	15.62
30-39	1	3.12
40-49	7	21.87
50-59	8	25.00
60-69	5	15.62
70-79	3	9.37
80-89	1	3.12

TABLE 14—*Age at Death of Nine Females and Twenty-Five Males in Whom Duodenal Ulcer Was Found at Necropsy*

Age	Males	Females
1-9	1	0
10-19	1	0
20-29	3	2
30-39	1	0
40-49	5	2
50-59	6	2
60-69	5	0
70-79	0	3
80-89	1	0

TABLE 15—*Ages of Ninety-Five Patients Operated on for Duodenal Ulcer (From Moynihan, 1913)*

Ages	Number of Cases	Per Cent
1-20	0	0
21-30	19	20
31-40	25	26
41-50	33	35
51-60	14	14
61-70	4	4

thirty-two cases with open ulcers exactly 75 per cent were over 40. In the third table, when the sexes are separated the period from 40 to 70 again is the large one while the females are strung along with no particular grouping. Moynihan's table is probably nearer the truth as to the incidence of duodenal ulcer, but our table brings out the fact that there is a considerable group of patients over 40 years without the benefit of surgery. When the number of duodenal ulcers found in each age group is compared with the total number in the necropsy series dying in that group, it will be seen that there is an increasing proportion up to 90 years of age.

SUMMARY

In 7,700 necropsy records at Bellevue Hospital extending from 1904 to 1922, studied as to frequency, number, size, shape, location, color, sex and age in gastric and duodenal ulcer, it was found that gastric and duodenal ulcers taken together are less frequent than most of the published figures. This is owing to the low figures for gastric ulcers since duodenal ulcer frequency runs the same or a little higher than compared figures.

Tabulation of the number of gastric ulcers shows multiple ulcers in about 29 per cent. This compares closely with other figures. About half the duodenal ulcers are multiple, however, this is a higher proportion than we have been able to find in any other statistics.

The average longer measurement for single gastric ulcers is 2.35 cm. The size of the ulcers decreased in each group as the number of ulcers increased, with one exception. The duodenal ulcers ranged from less than 0.5 to 2 cm. in diameter. There was nothing noteworthy when these were grouped according to number of ulcers in a case.

Most of the gastric ulcers were described as round, rounded or circular, nearly 25 per cent were oval. Almost any shape is possible. Almost all the duodenal ulcers were oval or rounded.

Seventy-six per cent of the gastric ulcers were found near the pylorus, 12 per cent near the cardia, and 12 per cent in the midgastric zone. Of nine cases on the anterior surface three were near the pylorus, one (4 cm. away), three, 5 cm. away, and two were near the greater curvature (table 7). The duodenal ulcers were nearly all in the first portion of the duodenum. In seven cases of multiple ulcer the second portion was involved. Two cases of encircling ulcer extended to the second portion.

Two gastric and no duodenal ulcers were in colored persons. The gastric ulcers were in about three males to one female. The duodenal showed only slightly greater preponderance of males.

Of the 7,700 necropsies 760 were on patients between 60 and 69. Of these 27, or 3.5 per cent, had gastric ulcer. It is found that with the exception of the group aged from 30 to 39 and the 40 to 49 group, which are the same, the percentage of gastric ulcer increases to 70 years, when it falls, as it also does in the 80 to 89 group. The percentage of duodenal ulcers increases for each age group up to 90 years.

EDEMA

I CORRELATION OF ELASTOMETER FINDINGS, DISAPPEARANCE TIME FOR INTRADERMALLY INJECTED SALT SOLUTION, URINALYSIS AND NITROGEN RETENTION OF THE BLOOD IN EDEMA

MARGARETE META KUNDE, PH D
CHICAGO

The rapid disappearance, in children with edema, of the cutaneous elevation produced by intradermal injection of 0.2 cc of 0.8 per cent salt solution was described by McClure and Aldrich¹ in 1923. They suggested that this test might be of value for detecting disturbed water balance in the tissues, and for following the progress of such disturbance. Later these authors² reported this test to be a valuable method for determining immediate prognosis of conditions in children characterized by generalized edema, with albumin, casts and, in some cases, red blood cells in the urine, but unassociated with nitrogen retention in the blood. They also reported the test to be an aid in directing the therapeutic management of these cases. Baker³ stated that in scarlet fever and diphtheria the disappearance time of intradermally injected salt solution is reduced in proportion to the severity of the intoxication and that the test aids in arriving at a prognosis of these diseases. Harrison⁴ reported shortened disappearance time in lobar pneumonia in children with a slow return to normal after crisis and with no constant relationship between the height of the fever and the length of the disappearance time. The normal disappearance time is considered as being longer than one hour for children, and somewhat longer still for adults. In this paper we deal only with adults.

As the edema described by McClure and Aldrich was determined by tactile estimation (a method of questionable delicacy) it seemed advisable to correlate the disappearance time of the intradermally injected salt solution with findings obtained by the use of Schade's⁵ elastometer

* From the Otho S. A. Sprague Memorial Institute and the Pathological Laboratory of the Cook County Hospital.

1 McClure, W. B., and Aldrich, C. A. Time Required for Disappearance of Intradermally Injected Salt Solution, *J. A. M. A.* **81** 293-294 (July 28) 1923.

2 Aldrich, C. A., and McClure, W. B. Intradermal Salt Solution Test, Its Prognostic Value in "Nephritis" with Generalized Edema, *J. A. M. A.* **82** 1425-1428 (May 3) 1924.

3 Baker, W. J. Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, *J. A. M. A.* **83** 1566-1567 (Nov 15) 1924.

4 Harrison, Jeanette. Intradermal Salt Solution Test in Lobar Pneumonia in Children, *J. A. M. A.* **84** 1258-1259 (April 25) 1925.

5 Schade, H. *Ztschr. f. exper. Path. u. Therap.* **11** 369, 1912.

Schwartz ⁶ and others ⁷ found that by means of this instrument one could detect degrees of edema not appreciable by the palpating finger, and at the same time secure a graphic quantitative record of the condition. Our results confirm this statement. It is impossible to express in mathematical terms the degree of edema present, as determined with the elastometer, because the height of the curve depends entirely on the closeness of contact that the disk bearing the weight makes with the surface of the skin. However, the character of the curve and the deficiency of return to the base line gives an objective index of the approximate amount of edema, not accurately obtainable with the palpating finger. It must be remembered, in this connection, that the elastometer gives no information as to the generalization of the condition of edema. It is an index only of the edema in the exact area to which the tactile disk is applied, just as is the case with the palpating finger. But the elastometer furnishes a means for producing an objective

TABLE 1—*Elastometer Findings, Disappearance Time for Intradermally Injected Salt Solution and Body Temperature in Typhoid Fever Without Palpable Edema **

Case	Date	Elastometer Findings on Dorsum of Wrist	Widal Reaction	Body Temperature Fahrenheit	Disappearance Time for Intradermally Injected Salt Solution
1 (A B)	7/30	0	+	100.2	65 minutes
2 (S M)	8/11	0	±	102.0	1 hour, 15 minutes
3 (J A)	8/12	0	+	100.2	1 hour, 15 minutes
4 (K L)†	9/ 2	0	Negative	99	35 minutes
5 (S T)	9/25	0	±	100	1 hour, 25 minutes
6 (I C)	9/26	0	+	100.8	1 hour, 15 minutes
7 (I N)	9/26	0	+	104.8	1 hour, 25 minutes

* Urinalysis of the cases showed no albumin, blood or casts.

† Typhoidal thrombophlebitis was suspected.

record, thereby eliminating error due to differences in the ability of individuals to discriminate between different degrees of pitting and between slight pitting and normal elasticity of the skin, and it records degrees of edema too slight to be detected by palpation.

In this report, all elastometer curves and intradermal salt solution tests are made on the dorsum of the wrist unless otherwise stated. The technic for using the elastometer is described by Schwartz ⁶. Our purpose in this work is to determine what relationship, if any, exists between the disappearance time of intradermally injected salt solution, elastometer findings, body temperature, nitrogen retention in the blood and pathologic urinary findings.

Table 1 gives the results obtained from seven cases of typhoid fever. Six of these show a normal length of time for the disappearance of

6 Schwartz, A. B. Edema, Arch. Int. Med. **17**: 396-404 (March) 1916.

7 Mayer, Mary E. and Schwartz, A. B. Edema in Pneumonia. Arch. Int. Med. **17**: 459-464 (April) 1916. Schade (Footnote 5).

intradermally injected salt solution although the body temperature of the patients ranges from 100.2 to 104.8. Urinalysis at no time showed albumin, casts or blood. The elastometer curves, as seen in figure 1, show no edema, except a very slight degree in case 4 (K L). Here the disappearance time was also reduced but the patient was suffering from thrombophlebitis of the leg as well as from a condition suspected as being typhoid. No pitting could be detected at the ankles with the palpating finger. These results indicate that increase in body temperature up to 104.8 does not of itself shorten the disappearance time for intradermally injected salt solution, also that in uncomplicated typhoid fever there may be no tendency toward edema as determined by the elastometer.⁸

Table 2 shows the results obtained from a group of seven women in the pathologic obstetric ward. All were suffering from acute toxemia of

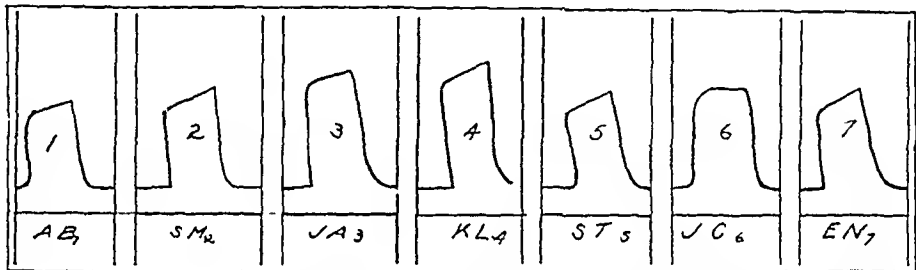


Fig 1—Absence of edema in uncomplicated typhoid, when there was no shortening of disappearance time of intradermally injected salt solution. An elastometer curve obtained from a nonedematous person with normal elasticity of the skin shows a tendency to plateau formation of the horizontal phase with prompt return to the base line of the down stroke. All curves in this figure, except curve 4, have the characteristics of curves obtained from normal individuals. Curves 1, 2, 3, 4, 5, 6 and 7 were obtained from patients with typhoid fever (table 1), the disappearance time for intradermal injected salt solution was slightly shortened in case 4 (K L, curve 4), curve 4 shows slight edema, the typhoid here is complicated by thrombophlebitis of the leg.

pregnancy, with or without eclampsia. The disappearance time of the intradermally injected salt solution was markedly short in all cases except case 3 (A B), in which shortening, though present, is less pronounced. This effect of the toxemias of pregnancy on the disappearance time has also been shown by Lash⁹ with patients from the same ward. Slight palpable edema at the ankles could be detected in cases 1 (R B), 3 (A B) and 4 (V L), a condition probably due in part to pressure by the gravid uterus on the pelvic vessels. In these three cases and also in case 5 (L W), edema could be detected at the dorsum of the wrist by means of the elastometer (fig 2), but could not be detected by palpation.

⁸ A series of cases of typhoid fever was also tested by S. A. Leader, who likewise found no decrease in the disappearance time.

⁹ Lash, A. F. Surg. Gynec. Obst., to be published.

The urine of this group, except case 2 (O N), is characterized by a large content of albumin and in some cases the presence of casts. Blood chemical findings in the four cases analyzed show some nitrogen retention, but the amount of nitrogen retention bears no relationship to reduction in disappearance time of the intradermally injected salt solution. The elastometer curves may return to normal several days or weeks before the return to normal of the disappearance time for intradermally injected salt solution. The findings in this group suggest that when the disappearance time is short and no palpable edema is demonstrable, slight edema may in some cases be detected with the elastometer. But in other cases the shortened disappearance time is the only index obtainable of a disturbed water balance in the tissues.

TABLE 2—Data on Cases of Toxemia of Pregnancy

Case	Date, 1925	Urinalysis		Blood Chemistry					Palpable Edema Region Most Marked	Elastometer Findings on Dorsum of Wrist	Disappearance Time for Intradermally Injected Salt Solution, Minutes
		Albumin	Casts	Total Nitrogen	Non protein Nitrogen	Urea Nitrogen	Creatinine	Uric Acid			
1 (R B)	3/29	++++	+	2 660		18 60	1 5	3 9	Ankles	Slight edema	10 20
	3/31	++++	+	2 758	42 30				Ankles	None	20
	4/ 5	++++	+						Ankles	None	50
	5/15	+	0						None	None	45
2 (O N)	3/28	0	0	2,800		11 64	1 43	1 76	None	None	25
	4/24	0	0						None	None	40
3 (A B)	3/24	++++	++		39	19 00	1 47	1 6	Ankles	Slight edema	50
	4/ 2	0	0	2 390	30	11 2			None	None	50
	4/ 6	0	0						None	None	50
4 (V L)	4/21	++++	+						Ankles	Slight edema	10
	5/ 1	+	0						None	None	30
5 (L W)	5/12	++	+						None	Slight edema	14
6 (T G)	6/ 6	++	0						None	None	30
7 (J S)	5' 1	++++	0						None	None	40

Widal¹⁰ has stated that 6 Kg. of water may be retained in the adult before pitting can be detected. These cases with shortened disappearance time and no manifestations of edema may be cases in which the amount of water retention is not sufficient to be detected even with the elastometer, but in which a disturbed water balance is an active process, as indicated by the short disappearance time. This disturbed water balance in some instances may lead to edema demonstrable with the elastometer, in others, the process may be interrupted, resulting in a lengthening of the disappearance time and return to a normal water

10 Widal, F, and Lemierre, A. *Ergebn der inn Med u Kinderh* 4 523, 1909

balance of the tissues before a retention sufficient to be detected with the elastometer has occurred. Or again, shortened disappearance time without edema may mean that the tissues have an increased affinity for water, but that for some reason water is not available to satisfy this increased affinity.

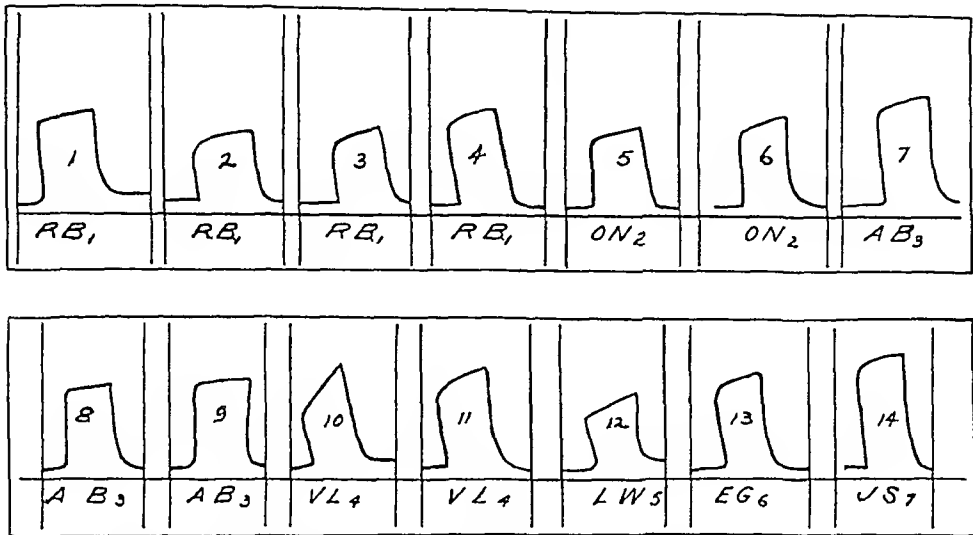


Fig 2—Fourteen elastometer curves from seven cases of toxemia of pregnancy (table 2), no edema could be detected with the palpating finger, but the elastometer shows edema in curves 1, 10 and 12 by the deficient return of the down stroke to the base line, a loss of elasticity is indicated in curves 10 and 12 by the sharp inclination of the horizontal line, the time for the salt solution test is markedly reduced in all these cases except case 3 (A B), curves 7, 8 and 9 were obtained from this patient.

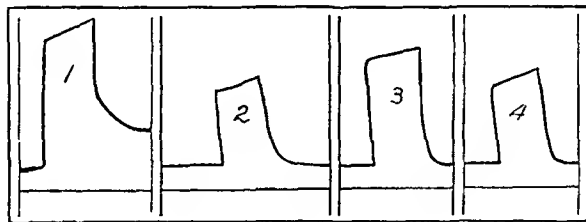


Fig 3—Curves obtained during critical period and period of recovery of patient 1 (C N) with acute nephritis. The elastometer ceases to give evidence of edema three weeks before the disappearance time is normal. Curve 1, March 22, shows marked edema, with disappearance time fifteen minutes, curve 2, March 30, no edema, with disappearance time from twenty to twenty-eight minutes, curve 3, April 29, no edema, with disappearance time from forty-five to fifty minutes, and curve 4, May 15, no edema, with disappearance time fifty minutes.

Table 3 shows the results obtained from fifteen cases of nephritis, one case of edema due to cardiac decompensation, one case of nutritional edema, one case of localized edema supposedly due to lymphatic obstruction, one case of bichloride of mercury poisoning, and three cases of hypertension. Cases 1 to 9, inclusive, are characterized by a reduced disappearance time, albumin in the urine in all except case 7 (T D).

and, in some cases, blood and casts Nitrogen retention in the blood is marked in some cases, slight in others The cases of acute nephritis studied most extensively need separate discussion because of their different clinical courses and terminations

During the time that the condition was grave case 1 (C N) had a disappearance time of fifteen minutes Edema was marked and generalized As the edema subsided the disappearance time lengthened a little but remained markedly reduced several weeks after edema could no longer be detected with the elastometer (fig 3) The presence of

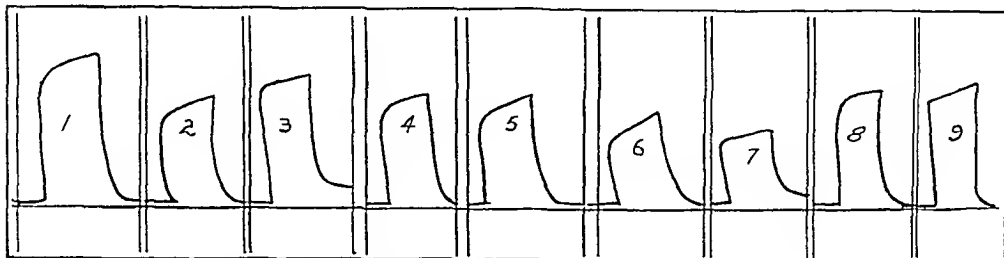


Fig 4—Elastometer curves obtained from patient 2 (J C) with acute nephritis with no marked palpable edema over dorsum of wrist The disappearance time at the dorsum of the wrist was never less than twenty minutes, curves 1, 2, 4, 5, 6, 8 and 9 show no edema At the time these curves were made the disappearance time was from thirty-one to fifty-five minutes, curve 3 shows slight edema, with disappearance time twenty minutes

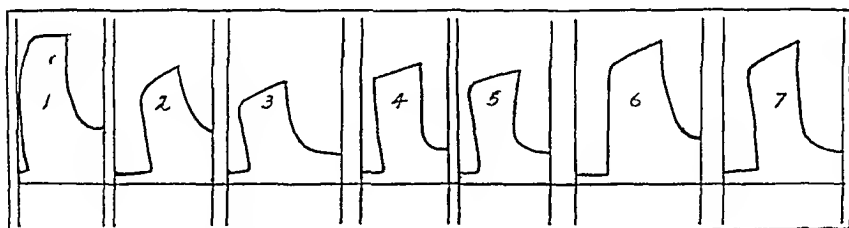


Fig 5—Curves obtained from patient 3 (J S) with acute nephritis and very marked palpable edema The patient did not recover, the disappearance time persistently remained less than ten minutes, except the day that curve 4 was obtained, July 30, 1925, when the disappearance time was thirty minutes

albumin and casts in the urine and nitrogen retention in the blood bear no relationship to the length of the disappearance time or the character of the elastometer curve After the disappearance time increased to thirty minutes no edema could be detected with the elastometer This same condition holds in case 2 (J C) (fig 4) Both these patients made a complete recovery

In case 3 (J S), acute nephritis with marked edema and fatal termination, the disappearance time during the entire course (from June 4 to July 19), except one test, was reduced to eight and ten minutes The elastometer showed marked edema (fig 5) which never

subsided. Urinalysis shows albumin, blood and casts. There also was nitrogen retention in the blood.

Figure 6 shows elastometer curves obtained from patient 5 (G T) with acute mercurial poisoning. Curve 1 was obtained about two and one-half hours after the sublimate had been swallowed. During this time the patient had been brought to the hospital and the usual antidotes were effectively administered. The disappearance time was normal (sixty-five minutes). No edema could be detected with the elastometer. Urinalysis showed no albumin, blood or casts. Two days later the disappearance time was reduced to thirty minutes, and remained so

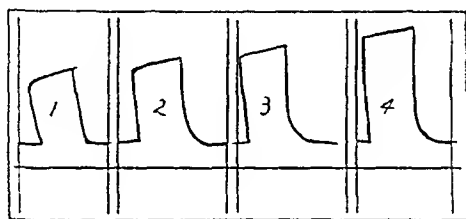


Fig 6—Curves in case 7 (G T) of acute mercuric chloride poisoning. Curve 1 shows no edema, with disappearance time sixty-five minutes, curves 2, 3 and 4 show no edema, with disappearance time thirty minutes. The lessened disappearance time is the only indication of disturbed water balance in the tissues.

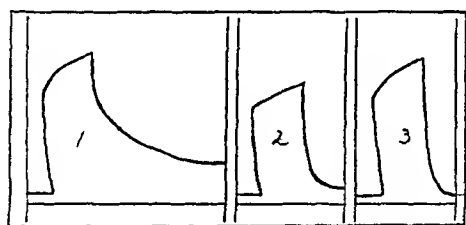


Fig 7—Curves of case 7 (T D) of generalized palpable edema due to cardiac decompensation, in this case the disappearance time returned to normal, as soon as the demonstrable edema disappeared. Curve 1, July 27, shows marked edema, with disappearance time from two to three minutes, curve 2, August 1, slight edema, with disappearance time twenty-five minutes, and curve 3, August 3, no edema, with disappearance time sixty minutes.

during the following week, at the end of which time the patient was discharged from the hospital. No edema could be detected with the elastometer during this period of shortened disappearance time. This again is a case in which the reduced disappearance time is the only obtainable evidence of disturbed water balance in the tissues.

In case 7 (T D), generalized edema due to cardiac decompensation, the disappearance time was from two to three minutes, during the period of most marked edema, but in less than a week of rest in bed and medication the edema had completely subsided. In this case the disappearance time became normal as soon as the edema could no longer be demonstrated (fig 7) by the elastometer. This is a striking contrast

to the picture in acute nephritis in which the disappearance time may remain shortened weeks after the elastometer curve is normal

The effect of localized edema on the character of the elastometer curve is shown in figure 8. The disappearance time over the area of localized edema is fifteen minutes. These curves were obtained from the ankles of a man, patient 11 (M C P), with marked edema of the right leg, believed to be the result of lymphatic obstruction, no 1 being from the normal leg, disappearance time one hour and twenty-five minutes, and no 2 from the edematous leg

Studies made on patient 12 (H) demonstrate clearly that the reduction in disappearance time precedes the ability to detect edema with

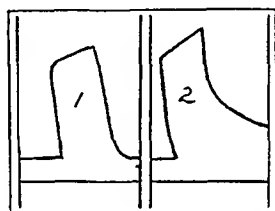


Fig 8—Influence of localized edema on character of elastometer curve in case 11 (M C P). Curve 1 was obtained from normal left leg, with disappearance time one hour and twenty-five minutes, curve 2, obtained from right leg, shows edema due to localized lymphatic obstruction, with disappearance time of fifteen minutes

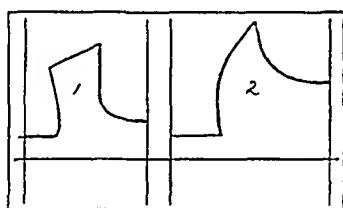


Fig 9—Nutritional edema in case 12, a decreased disappearance time precedes the ability to demonstrate edema with the elastometer. The disappearance time on the dorsum of the wrist gradually lessened from fifty-five minutes, June 30, 1925, to thirty minutes, July 10, 1925, no edema was demonstrable at the dorsum of the wrist by the elastometer until July 10, 1925 (curve 1), curve 2 shows edema at the leg on that day, when the disappearance time was four minutes

the elastometer (fig 9). This subject, a man, aged 36, voluntarily undertook for another study a total fasting experiment extending over thirty-three days and resulting in marked edema during the week following the termination of the experiment. Before the experiment was begun, May 27, 1925, the disappearance time at the dorsum of the wrist was one hour. At the end of the experiment, June 30, 1925, the disappearance time at the wrist was fifty-five minutes, at the leg, forty-five minutes, there was no pitting of the arm and slight pitting of the legs. July 2, the disappearance time on the dorsum of the wrist was fifty-five minutes, of the leg, thirty minutes. July 7, it was forty minutes at the

wrist and eight minutes on the leg. At this time there was marked palpable edema of the leg, but none of the arm. July 10, the disappearance time at the wrist was thirty minutes, on the leg four minutes. On this day edema of the arm could be detected by the elastometer for the first time. These findings at the wrist unquestionably prove that a shortening of the disappearance time precedes the ability to detect edema with the elastometer.

Figure 10 illustrates elastometer curves obtained from a group of eight cases of chronic nephritis without edema, with and without hypertension, and one case of arteriosclerotic hypertension, case 21 (M. A.). The disappearance time for the intradermally injected salt solution is normal in this group of cases, urinalyses show albumin in all except case 21 (M. A.). In some cases nitrogen retention in the blood also is marked (case 16, D. M. C., table 3). The elastometer curves show no evidence of edema. Evidently, then, albuminuria and nitrogen retention may occur without the existence in the skin of the

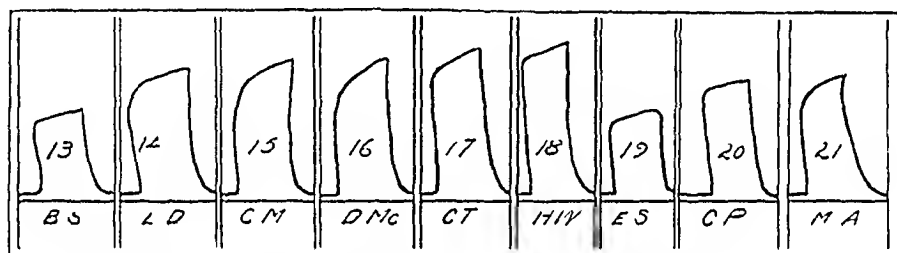


Fig. 10—Curves obtained from eight patients with chronic nephritis and one with hypertension, no edema could be detected with the elastometer, the disappearance time was normal, nitrogen retention of the blood was marked in some cases, albumin appeared in the urine of all (table 3), excepting case 21, M. A.

changes usually associated with edema, that is, shortened disappearance time and loss of elasticity.

SUMMARY

- 1 In uncomplicated typhoid fever, no edema was demonstrable with the elastometer. The disappearance time for intradermally injected salt solution was normal, although the body temperatures in the cases studied ranged from 99 to 104.8.

- 2 In acute toxemias of pregnancy the disappearance time was reduced to approximately ten minutes before edema could be detected with the elastometer of Schade.

- 3 In acute nephritis the disappearance time fell to thirty minutes or less before edema could be detected with the elastometer.

- 4 In a series of cases of chronic nephritis with albuminuria and nitrogen retention, no edema could be demonstrated with the elastometer and the disappearance time for intradermally injected salt solution was normal.

TABLE 3—Data in Cases of Nephritis and Related Conditions

Case	Date, 1925	Palpable Edema Region Most Marked	Wrist is Determined by Flis- tometer	Disap- pearence Time for Intra dermal Salt Solution Test at the Wrist, Minutes	Blood Chemistry					Clinical Diagnosis	Remarks	
					Urea		Non- protein Nitro- gen	Ure- nitro- gen	Uric Acid			Cac- etamine
					Al- bumin	Blood						
1 (CN)	3/22	Generalized	++	15	++	0	39	18	1.5	Acute nephritis	Condition improving Marked improvement Discharged from hospital	
(CN)	3/30	Lower extremities	++	25-28	++	0		49.9	2.9			
(CN)	4/21	Ankles	++	15-50	++	0		51.9	1.5			
2 (CN)	5/15	Slight at ankles	0	50	0	0	24			Acute nephritis		
(CN)	3/23	None	0	55	++	++						
(JO)	4/20	Over lumbar vertebrae	0	30	++	++						
(JO)	3/8	Over lumbar vertebrae	+	20-25	++	++				Acute nephritis		
(JO)	5/18	Over lumbar vertebrae	0	40	++	++						
(JO)	6/18	Ankles	0	50	++	++						
(JO)	7/13	Ankles	0	50	++	0						
(JO)	8/23	Face and legs	+	30	++	0						
(JO)	9/2	Ankles	++	55	++	++	28	10.2	1.7			
(JO)	9/13	Ankles	0	55	++	++	38		2.5	Acute exacerbation of chronic nephritis	Condition unimproved	
(JO)	6/1	Markedly generalized	++	5-7	++	++	68.9	17.2	3.85			
(JS)	6/19	Markedly generalized	++	10	++	++						
(JS)	6/20	Generalized but not so marked	++	10	++	++					Sent home Returned to hospital	
(JS)	7/13	Lower extremities	+	30	++	++	73	17.1	3.53			
(JS)	7/14	Generalized	++	5-8	++	++						
(JS)	7/19	Markedly generalized	++	6-8	++	++				Parenchymatous nephritis Mercuric chloride poisoning	Marked disappearance of edema Condition much worse Died	
4 (GT)	6/8	Generalized	++	10	++	++						
5 (GT)	8/1	None	0	65	0	0						
(GT)	8/3	None	0	30	+	+					Sent to psychopathic hos- pital	
(GT)	8/7	None	0	30	0	0						
(GT)	8/8	None	0	30	0	0						

Case	Date, 1925	Palpable Edema Region Most Marked	Edema on Dorsum of Wrist is Determined by Elastometer	Disappearance Time for Intradermal Salt Solution Test at the Wrist, Minutes	Urinalysis			Blood Chemistry				Clinical Diagnosis	Remarks	
					Albunin	Blood	Casts	Non-protein Nitrogen	Urea Nitrogen	Urea	Creatinine			
6 (M B)	6/20	Markedly generalized	++	8	+++	0	++						Acute exacerbation of chronic nephritis	
7 (T De)	7/27	Markedly generalized	+++	2-3	0	0	0						Cardiac decompensation	
8 (T De)	8/1	Lower extremities	+	25	0	0	0							
8 (S F)	8/3	Lower extremities	0	60	0	0	0							
	9/23	Generalized	+	14	+	0	0	36.8	33.9	1.5			Chronic parenchymatous nephritis	Sent home Cardiac complications, systolic blood pressure, 220, diastolic, 180
9 (L S)	9/25	Lower extremities	+	25	++	0	++	36.2	33.95	1.5			Acute exacerbating chronic nephritis	
10 (E B)	9/15	Ankles	+	45	+	0	0	13.07	1.90	1.44			Hypertension, cardiac hypertrophy	Systolic blood pressure 230, diastolic, 100
11 (M O P)	6/3	Right lower leg only	++	15*	0	0	0						Localized obstruction of lymphatics	Absorption time of right lower leg, 5 minutes
12 (H)	7/2	Lower extremities	0	55	0	0	0	35	32.9	3.8	1.5		Nutritional edema	Cutaneous complication
13 (H)	7/10	Generalized	+	30	0	0	0							
13 (B S)	8/17	Slight at ankles	0	75	++	0	+	27	71.9	3.2	3.0		Chronic nephritis	
14 (L D)	8/20	None	0	75	++	0	0		9.3	1.28	1.2		Chronic nephritis, arterial sclerosis	
15 (L D)	8/28	None	0	75	++	0	0	20.5		2.6	1.5		Chronic nephritis	
15 (C M)	5/27	None	0	60	+++	0	0						Chronic nephritis	
16 (D M G)	8/19	None	0	70	++	0	0		88	3.1	3.7		Chronic nephritis	
17 (D M O)	9/6	None	0	75	++	0	0		51	3.1	1.7		Chronic nephritis	
17 (C T)	8/21	None	0	60	++	0	+		21	2.1	1.6		Chronic nephritis	
18 (H W)	9/20	Ankles	0	85	++	0	+		23	3.3	1.6		Chronic nephritis	
19 (E S)	9/21	None	0	75	++	0	+		34.5				Chronic nephritis	Systolic blood pressure, 100, diastolic, 80
20 (O P)	8/18	None	0	85	+	0	0	28.02		2.3	2		Chronic nephritis	Systolic blood pressure, 210, diastolic, 165
21 (M A)	9/16	None	0	75	0	0	0						Hypertension, arterial sclerosis	Systolic blood pressure, 250, diastolic, 100
22 (M O)	9/19	Ankles	+	30	0	0	0	37	16.8	1.85	1.5		Hypertension, chronic myocarditis, arteriosclerosis	Systolic blood pressure, 250, diastolic, 100

* In this case the disappearance test was made over edematous part of right leg. The disappearance time of the corresponding area on the left leg was one hour and thirty minutes.

5 Conditions causing the appearance of albumin and casts in the urine and nitrogen retention in the blood are not necessarily causal factors in shortening the disappearance time for intradermally injected salt solution

6 A decrease in disappearance time precedes the ability to detect edema with the elastometer

7 In acute nephritis with disappearing edema the elastometer curve becomes normal several days or weeks before the disappearance time becomes normal. In edema due to cardiac decompensation the disappearance time may become normal as soon as the edema has subsided, as determined by the elastometer

8 That both the elastometer curve and the disappearance time for intradermally injected salt solution are markedly influenced by conditions in localized areas¹¹ must be taken into consideration in using these tests as an index to generalized conditions. For comparative work the two tests must be made over the same area

11 Cohen, M. B. Intracutaneous Salt Solution Test. Preliminary Report of Simple Method for Determining Efficiency of Circulation in Extremities, J. A. M. A. 84 1561 (May 23) 1925

STENOSIS OF THE ISTHMUS (COARCTATION) OF THE AORTA AND ITS DIAGNOSIS DURING LIFE

REPORT OF FOUR CASES^{*}

JOHN T KING, JR., M D

BALTIMORE

Congenital cardiovascular lesions are, as a rule, multiple, they present confusing physical signs and are apt to produce a number of different diagnoses. Coarctation (congenital stenosis) of the aorta produces outspoken clinical signs, which, when present in characteristic form, may be recognized at a glance.

It is a curious fact, however, that the diagnosis is rarely made during life. Case 1 of this series was the only case on record in the Johns Hopkins Hospital case histories during the first thirty-four years of its existence (1889-1923). Since that time three additional cases have been found in the wards and outpatient departments of this hospital, and we are inclined to believe that other patients with this condition may have gone through our hands unrecognized because of the lack of familiarity with the clinical picture, or possibly because of the lack of outspoken physical signs. This impression is strengthened by post-mortem reports, which show that coarctation of the aorta is not uncommon, for example, Fawcett¹ found eighteen cases of coarctation in a routine postmortem examination of 22,316 persons, or almost one per thousand. The diameter of the aorta at the site of the stenosis varied from one-half inch (1.27 cm) to a narrow opening that barely admitted a fine probe, while in one case there was total obliteration of the aorta. No case in Fawcett's series had been recognized during life.

It would be of no especial interest to attempt to summarize the reported cases of coarctation since this has been done particularly well from time to time. For this reason Abbott² believes that the twelve cases analyzed by her in 1915 probably represent the total number of cases recognized during life and postmortem more nearly than is the case with reports of other congenital cardiovascular lesions. A recent bibliography has not been found in the literature, and we have tried to compile one that includes most of the reported cases.

^{*} From the medical clinic, Johns Hopkins University Medical Department

¹ Fawcett, John. Coarctation of the Aorta, as Illustrated by Cases from the Postmortem Records of Guy's Hospital from 1826-1902, *Guy's Hosp Rep* **59**, Series 111, **44** 1, 1905

² Abbott, M. Osler and McCrae's Modern Medicine, Philadelphia, Lea and Febiger, 1915

An excellent analysis of cases of generalized narrowness of the aorta prior to 1901 was made by Burke,¹⁰ who found seventeen of twenty cases in men, three in women. The average life of his patients was 23.8 years; this is approximately the age described by all writers on the subject as the critical adult age. Most patients die of myocardial insufficiency. Burke found that symptoms had existed for less than one year before death in thirteen cases, for three years in one case, since childhood in five cases, and for an undetermined period in one case. Intermittent claudication occurred in only one case. The symptoms were characteristically rather sudden and were those of typical myocardial insufficiency. There were no blood pressure determinations. In the same year von Minkowski¹¹ compiled 120 cases of stenosis of the isthmus of the aorta, and reported a case recognized during life, including an excellent clinical description; he found aortic insufficiency with coarctation, blood pressure in the arms 300 +, absence of pulsation in the tibial and peroneal arteries, and barely palpable pulsation in the femorals, which allowed no determination of leg blood pressure. He gives a good description of the collateral circulation, recognizing the prominent pulsation of the transversalis colli arteries, of the dorsal scapular arteries in the interscapular region, and the dilatation of the mammary arteries at the xiphoid; he also described systolic murmurs in the interscapular region near the spine.

Aortic insufficiency is often associated with coarctation; disease of the aortic valves was found in ten of Fawcett's¹ eighteen cases. In many cases (probably a majority of cases) the aortic insufficiency is recognized and the coarctation is passed over. Unfortunately for the clinician, increased vascular pulsation occurs in each condition, when present, such pulsation is probably attributed to the aortic insufficiency which acts in this way in many cases as a mask for the coarctation.

REPORT OF CASES

CASE 1—*Coarctation of the Aorta*

M. P., a single man, aged 35, an Italian laborer, came under observation in the outpatient department of the Johns Hopkins Hospital, May 5, 1908.

The parents were living and well. Of two sibs, one was living and well, one died of unknown cause. There was no history of tuberculosis or cancer.

The patient's general health had been good. He had had an occasional attack of fever, lasting two or three days, since childhood. He thought that he had not had measles, pertussis, mumps, scarlet fever, rheumatic fever, diphtheria, chorea, malaria, typhoid, pneumonia or pleurisy. He had an attack of rheumatism in 1906, being confined to bed for three days. He suffered from a chronic nasal obstruction, and had an occasional sore throat. Adenoidectomy of a large mass of tissue had been performed, Aug. 8, 1913. In November, 1923, he was admit-

10 Burke Joseph. Ueber angeborene enge des aorten systems, Deutsches Arch f Klin Med 71 189 1901

11 Von Minkowski. Stenose der Aorta an der Einmündungsstelle des Ductus Botalli. München med Wchnschr 48 1335, 1901

ted to the hospital for acute laryngitis. In January, 1924, a bilateral resection of the inferior turbinates was followed by bronchopneumonia, from which he made an uneventful recovery.

He had no chronic cough and no dyspnea that was not brought on by hard work, except in 1908, and again in 1913, when he had dyspnea rather easily for considerable periods. He had no bronchitis, sputum or hemoptysis. He suffered considerable palpitation after exertion in 1908. He had no edema and no pleural pain. The appetite and digestion were good. The bowels and habits were regular. He had no hemorrhoids, no abdominal pain, no hematemesis or melena. There were no bladder or kidney disorders except for nocturia (three or four times) which has been present since before 1908. No hematuria and no syphilis were noted, he had had gonorrheal infection without complications twice. The patient had suffered all his life from cramps in the hands and legs.

He did not use tobacco, and beer and wine only in moderation. He did hard labor on a railway in all kinds of weather.

On the first visit to the outpatient department in 1908, the patient complained of pain in the right side of the chest. A year before this he had developed a marked pain in the left side of the chest when he worked hard or ran. He had been dyspneic on exertion during this year, and had noticed palpitation of the heart on exertion. The pain in the right side of the chest was noticed only while working, it was sharp and stabbing in character, causing him to stop work. He had had nocturia four or five times as long as he could remember.

Physical examination in 1908 showed a well nourished boy, of good color, the mucous membrane and the conjunctiva were of good color. The tongue was clean and teeth fair. The pupils were equal and reacted to light and accommodation. The pulse was 72, regular, of good volume and normal tension. The radial artery was slightly thickened. The pulses were equal. The neck was normal in pulsation. The thyroid was normal, and there was visible pulsation above and below the clavicle, especially on the left side, but also on the right. The chest was well developed, the costal angle being under 90 degrees.

In the heart the precordial pulsation was visible in the left second and third intercostal space, and on the right side next the sternum in the second intercostal space. The point of maximum impulse was extremely visible in the fifth intercostal space, about 1 cm. inside the nipple line. There was no thrill, and the boundaries were normal. The first sound at the apex was prolonged, the second was sharp and snapping. In the pulmonic area a prolonged systolic murmur was followed by a snapping second sound. A systolic murmur in the aortic area was transmitted up to above the clavicle, followed by a sharp snapping second sound. There was no thrill in the aortic area and no heaving in the back. In the region of the second dorsal vertebra was the most intense blowing murmur, which corresponded to the systole of the heart. A slight pulsation was felt to the right of this vertebra, but it was not visible except in a certain oblique light. No especial dulness was noted over this area. No shock was felt. The lungs were clear. The abdomen was normal. No sugar or albumin was found in the urine.

The condition was recognized as coarctation of the aorta by Dr. T. McCrae in the outpatient department, the patient was admitted to the hospital, where the following data were obtained:

Blood analysis (1908) showed hemoglobin, 90 per cent, white blood cells, 8,000, and red blood cells, 5,120,000. The differential count was: polymorphonuclear neutrophils, 68.8 per cent, large mononuclears, 5.2 per cent, small mononuclears, 18.4 per cent, transitionals, 5.2 per cent, eosinophils, 1 per cent, nucleated red blood cells, 0.2 per cent, mast, 0.2 per cent, and unclassified, 1 per cent.

Fluoroscopic examination of the chest (1908) by Dr. F. H. Baetjer was negative. The blood pressure (1908) report was: "The pressure taken with the sphygmomanometer is equal to if not 5 mm. higher in the femorals than in the brachials." (In view of the subsequent blood pressure findings it seems likely that this note is in error.) The blood pressure (presumably systolic and in the brachial artery) was charted as 175, 155 and 180. An extract from Dr. L. F.

The cases included in this paper are reported to call attention to a condition that is unfamiliar to most physicians, to place the cases on record and to emphasize a few details of diagnosis

Coarctation of the aorta must be distinguished from other anomalies of the aorta, such as a generalized hypoplasia and the various other defects of the aortic arch. By true coarctation is understood a comparatively sharp constriction or more diffuse stenosis, sometimes a total obliteration, of that portion of the thoracic aorta lying between the left common carotid artery and the entrance of the ductus botalli.

It should be remembered that this portion of the aorta, which is known as the isthmus, performs a minimal function during embryonic life, since the prenatal patency of the ductus botalli allows a considerable quantity of blood to pass directly into the aorta below the isthmus, while the vessels proximal to the isthmus supply all the upper part of the body. For this reason it is not remarkable that this portion of the aorta should be the site of persistent narrowness or even obliteration, when abnormalities of development occur. The so-called infantile type of coarctation, usually a rather diffuse narrowness of the isthmus—and usually fatal—is thought to be due to such an error in development. The adult variety, however, to which all of our four cases probably belong, consists of a rather sharp constriction of the aorta at or near the entrance of the ductus. It is thought to arise postnatally and is most reasonably explained by the skodaic theory. This theory explains the constriction of the aorta by assuming an extension of the tissue of the ductus into the adjacent wall of the aorta; it is thought that this tissue contracts after birth along with the tissue of the ductus botalli. In favor of the theory is the fact that the adult type of coarctation has not been noted before birth, against it is the fact that the isthmus begins normally to function fully at a time when the ductus is being obliterated; the obliteration of the ductus is aided by a marked drop in pressure behind it when the pulmonary circulation begins to function, while the isthmus is strained by a marked increase in blood volume passing through it, and a constriction developing in the face of such increased function is a theory difficult to grasp. We have, however, no better explanation to offer.

Priority in recognition of coarctation is given by Abbott² to Paris³ (1789). Meckel's⁴ case was apparently one of diffuse hypoplasia of the aorta, but Morgagni⁵ may have described in 1760 a case of true coarctation from a postmortem on a monk. Morgagni said "A short distance from the heart the aorta was contracted to an astonishing

3 Paris. Case of Considerable Contraction of the Aorta, translated into English by R. Gosling, London, *Chir d Desault* 11 107, 1789.

4 Meckel Johann. *Nachr d Acad d Wissensch*, Berlin, 1755.

5 Morgagni, G. B. *De Sedibus et Causis Morborum*, Epist XVIII, Art 6, 1760.

degree" Unfortunately, he failed to state definitely just where the aortic constriction in his case existed, or how sharply localized it was. Important early contributions were those of Stoll-Krotowski⁶ and Wernicke.⁷ The last named found five cases of coarctation diagnosed *intra vitam* prior to 1875 out of a total of sixty cases reported up to that time. He described the pathologic physiology as follows:

- 1 The superior intercostals anastomose with the intercostals from the aorta and carry blood into the aorta.

- 2 The transversalis colli arteries anastomose with the intercostals from the aorta and carry blood into the aorta.

- 3 The internal mammaries anastomose and carry blood into the intercostals, deep epigastric arteries, etc.

- 4 The innominate and left interscapular arteries are especially dilated.

Wernicke outlined the clinical syndrome as follows:

- 1 Collateral arterial circulation.

- 2 Pulsation in the interscapular area.

- 3 Dilated intercostal arteries.

- 4 Murmurs over the anastomotic vessels.

- 5 Discrepancy between the size of the pulse in the arms and that in the legs.

He also described the two critical periods of the condition which are recognized today, first, the period in infancy when the anastomotic circulation begins to develop and, second, the later myocardial strain imposed by the extensive collateral circulation. He found further that the condition was not incompatible with long life, one patient having attained the age of 92 years. The first American case appears to be that of Hutchinson,⁸ though I have not seen the report and it may have been, as many of the early cases were, an instance of hypoplasia of the aorta.

Total obliteration of the aorta occurred in fourteen of 105 cases of coarctation studied by Dickinson and Fenton⁹ in 1900, in a case of total obliteration found by them at necropsy and not recognized clinically, the collateral circulation was carried on through the internal mammary and first four intercostal arteries.

6 Stoll-Krotowski, M. *Stenosis aorte congenita*, Berlin, Gustav Lange, 1873.

7 Wernicke, R. *Die Verengerung und Obliteration der Aorta in der Gegend des Ductus Arteriosus Botalli und ihre Diagnose intra Vitam*, Berlin, Gustav Lange, 1875.

8 Hutchinson, J. H. *Constriction of the Aorta with Hypertrophy of the Heart*, *Hosp Med Gaz*, New York **6** 357, 1879.

9 Dickinson, W. L., and Fenton, W. J. *A Case of Complete Coarctation of the Arch of the Aorta*, *Necropsy*, *Lancet* **2** 1196, 1900.

Barker's note (1908) reads "Fair pulse in left dorsalis pedis artery, also palpable pulsation on the right Posterior tibials not felt Distinct pulsation in the radials and temporals Pulsation in the femorals barely felt Pulse in aorta barely felt on pressure above umbilicus Popliteal pulse not felt Distinct pulsation in internal mammary arteries" The tonsils and adenoids were removed

The urinalysis findings were light to orange color, specific gravity from 1.011 to 1.030, acid, sugar, 0, albumin, faint trace on admission, none later Microscopic examination showed a few hyaline casts on admission, none on several examinations later

A note by Dr T McCrae on the hospital record states that the diagnosis of coarctation of the aorta was made in the dispensary and later independently in the hospital (There was considerable discussion as to whether the patient had aneurysm or stenosis of the aorta)

July 10, 1913, the patient came to the dispensary with temperature of 100.1 and was admitted to the hospital, where a diagnosis of typhoid fever was made Before admission Dr Baetjer made a fluoroscopic examination of the patient and found "no sacular aneurysm Dilatation of the aorta, comparable to what one would expect to find in a man of 50" While the patient was in the hospital, there was apparently considerable discussion and consultation with the roentgenologic department as to the significance of the curious pulsation and systolic murmur in the left interscapular region The fever was due to single tertian malarial infection, from which convalescence was uneventful

May 23, 1917, roentgen-ray examination showed the heart and aorta to be normal Nov 26, 1923, the Wassermann reaction was negative, roentgen-ray examination of the heart and aorta was negative, the urine was normal March 19, 1924, I noted that the chief complaints during recent years had been pains in the arms and legs, especially on straightening them The patient had suffered over considerable periods with intermittent claudication of the legs, which limited his walking to one or two city blocks at a time, and caused him to give up work

March 19, 1924, his voice was much stronger The patient had recently had pneumonia following a nasal operation He complained now of frequent headaches, beginning in the early morning, and still had cramps in the legs at times but they were not so severe as formerly, he suffered from dyspnea only on hard work

My examination on this date follows There was no cyanosis There was marked pulsation visible in the carotids, subclavians, brachials and radials, also an area in each upper interscapular region in which a visible impulse was present The femoral pulsation was very small but was palpable on each side Neither posterior tibial was felt but there was pulsation in each dorsalis pedis artery, slightly reduced In the heart there was no shock or thrill The area of dullness was 9 cm to the left, 5 cm to the right There were no murmurs and sounds were normal There was a well marked systolic murmur heard over the areas of pulsation in the upper interscapular regions on both sides, it was transmitted downward over the descending aorta to about the sixth dorsal vertebra (fig 1) The pulse was 72, regular and bounding but not collapsing The systolic blood pressure in the right arm was 180, the diastolic 106, in the left arm, 180 systolic, 98 diastolic The blood pressure in the right leg (Tycos) and palpation of the dorsalis pedis were 110 systolic, in the left leg, 110

The Wassermann reaction on several occasions was negative

Jan 12, 1924, when the patient had just recovered from bronchopneumonia following a nasal operation, the carbon dioxide in the blood was 58.2 per cent by volume, creatinine, 1.36 mg per hundred cubic centimeters, uric acid, 3.81 mg per hundred cubic centimeters, red blood cells, 4,032,000, and hemoglobin, 75 per cent There was no leukocytosis after recovery

The blood pressure (presumably from the brachial artery) on this admission was 140 systolic 80 diastolic, rising gradually with improvement of the patient to 180 systolic, 95 diastolic

The points of interest in this case were

1 The presence of intermittent claudication which, though it might be expected because of the interference with the blood supply to points below the arms, is nevertheless rare Burke found it reported in only one of twenty cases in his series of generalized aortic hypoplasia

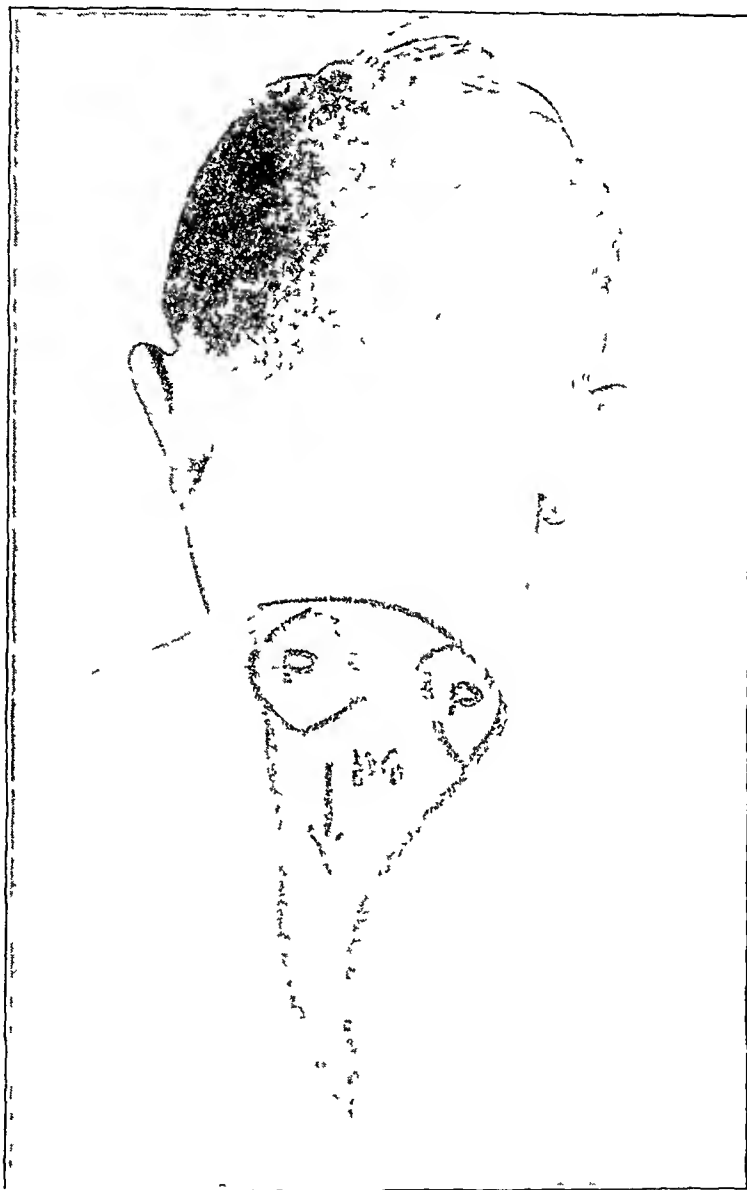


Fig 1 (case 1) —*P*, areas of systolic, aneurysm-like pulsations (dorsal scapular arteries), over larger zone, *M*, a systolic murmur was heard

2 The blood pressure was constantly higher in the right arm than in the left During the seventeen years in which the patient has been under observation the blood pressure in the arms has not changed

3 The patient worked for years in a railway gang, doing heavy work and being exposed to the weather

4 Nocturia (two or three times) had been present since childhood

CASE 2—Coarctation of the aorta, aortic insufficiency, arteriosclerosis, hypertension

P S, a white American man, aged 58, a carpenter, engaged in railway work, came under observation in the outpatient department of the Johns Hopkins Hospital, Jan 20, 1922, and to me, Aug 22, 1923. He complained of heart trouble.

The father died of heart trouble at 67. The mother died of childbirth. Two sibs were living and well. The family history was negative for cardiorenal disease, tuberculosis, cancer or nervous disease. Three children were living and well, one died in infancy, there was one miscarriage.

The patient had had none of the diseases of childhood, no typhoid fever, no pneumonia, no rheumatic fever. He had had malaria at the age of 25. He had an occasional sore throat. The eyes and ears were good, all the teeth had been removed.

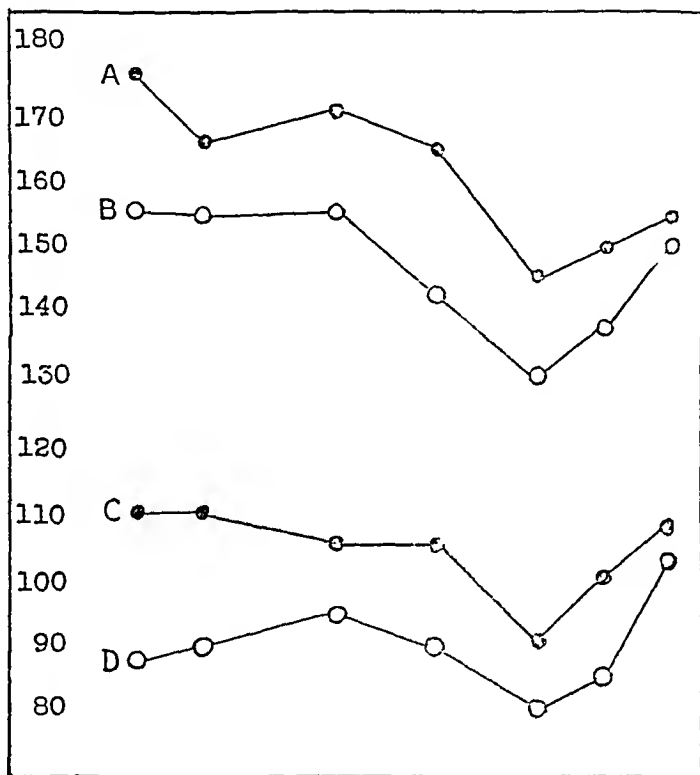


Fig 2 (case 1)—Systolic and diastolic pressures in arms, illustrating consistently higher pressure in right arm in this case. A, systolic pressure in right arm, B, systolic pressure in left arm, C, diastolic pressure in right arm, and D, diastolic pressure in left arm.

In 1919 the patient had a cough for three months, but no hemoptysis. The gastro-intestinal history was negative, except for occasional nausea from smoking. There was no constipation. He had suffered from nocturia (two or three times) for the last twenty-five years. There was no history of primary or secondary syphilis. He had some difficulty in starting the flow of urine. An epithelioma of the wrist was removed in 1916. The patient did heavy outdoor work.

Since 1916 he had had palpitation of the heart and extreme dyspnea, which rendered him unable to work at times.

Physical examination by me, Aug 22, 1923, revealed that the pain in the left shoulder had ceased and was now merely a sense of numbness. No dyspnea was noted. In addition to the marked pulsation of all the vessels of the upper extremities, the pulsation behind and the systolic murmur over the descending aorta, a very

striking diminution of pulsation in the legs was noted. There was no intermittent claudication. The signs suggested that aortic coarctation should be thought of.

October 24, the patient came in saying that he had no cardiac symptoms. The physical signs were as before. The patient's only complaint consisted of pain over an area the size of a silver dollar in the left supraclavicular fossa, corresponding to the remarkable pulsation that was still there. The pain was always caused by exertion, the patient said. The condition still suggested coarctation of the descending aorta or aneurysm. The roentgen-ray report was: lungs clear, aorta normal, and heart enlarged, particularly the left ventricle.

With the elimination of aneurysm from the diagnostic possibilities, I considered the patient to be suffering from coarctation of the aorta.

March 7, 1924, the patient felt well but still suffered from pain in the left shoulder when he worked, never when he was quiet. At night he "did not have cramps, but the legs were never comfortable on retiring and he was forced to stretch them frequently, or to get up and walk about."

The pupils were round, equal and reacted to light and accommodation. Extraocular movements were normal. The nose was normal. There was a plate in the upper jaw and he had pyorrhea about the few remaining teeth. The pharynx was normal. There were marked generalized arteriosclerosis and tortuous vessels. No gland trouble was noted. The lungs were clear on percussion and auscultation. No thrills or shocks were felt in the heart. The area of dulness was 10.5 cm to the left, 4 cm to the right. There was no retromanubrial dulness. The sounds were vigorous. There were soft apical systolic and diastolic murmurs, and a questionable presystolic gallop. The diastolic murmur was maximum in the fourth interspace over the body of the heart and less intense at the pulmonary area and the aortic area, it was heard nowhere behind. It was high pitched and whistling, with a distinct "pressure quality." Behind were marked pulsations as noted in the scapular region and a superficial dilated artery, with blood running from above downward, extending from the apex of the left axilla to the aortic area at the tenth rib. The pulsations in the scapular regions were marked, especially on the left, but were so large and deep that the course of the blood flow could not be determined. There was a pulsation at the eleventh rib on the left near the spine, apparently one of the intercostal arteries. A rather rough systolic murmur was heard over all the area of pulsation behind and along the aorta to the twelfth rib. The abdominal aorta was not palpable. Definite pulsations, not marked, were felt in the femoral, posterior tibial and dorsalis pedis arteries.

The blood pressure (Tycos) in the right arm was 210 systolic, 85 diastolic, in the left arm, 160 systolic, 85 diastolic. The blood pressure in the left and in the right leg was 142 systolic (by palpation) and 80 diastolic (by oscillation).

Roentgen-ray examination revealed the left border 13 cm and the right border 5.5 cm from the midsternal line.

March 28, 1924, the blood pressure in the right arm was 170/78, in the left arm, 155/70, and in the left leg, 102/90 (?). In the left leg there was no definite diastolic level, but a systolic level could be auscultated. Nothing was made out in the right leg on auscultation. All determinations on the arms and on the left leg were made with a mercury apparatus and by auscultation.

May 27, 1925, the patient complained of cramps in the legs in the mornings, especially on stretching. He felt quite well. The Wassermann reaction was negative.

An electrocardiogram, Dec 13, 1922, gave a rate of 65. The rhythm was sinoauricular, the P-R interval measured 0.18 second. The diagnosis was normal sinus rhythm.

The urine was clear and amber, with a specific gravity of 1.02, albumin, 0, sugar, 0. Microscopic examination revealed a few granular casts. There was a considerable number of white blood cells.

CASE 3—*Coarctation of the aorta, aortic insufficiency*

W R, a single, white American man, aged 55, a machinist, first came under observation in the outpatient department of the Johns Hopkins Hospital, Sept 15, 1916, complaining of nervousness and a queer feeling about the eyes. He thought the kidneys were diseased.



Fig 3 (case 2)—Areas marked in interscapular region represent limits of forcetul, aneurysm-like pulsation (the dorsal scapular arteries, probably anastomosing below with the intercostal arteries from the aorta and thus bridging the stenosis), the tortuous lines represent superficial arteries in which the flow is toward the aorta, these arteries fill readily from either direction but a pulsation is visible in them only when the blood enters from the outer end.

The father was living and well. The mother died of an unknown cause (cancer?).

The patient had measles, chickenpox and mumps as a child. He had no typhoid, but had malaria in 1902. The history was suggestive of arthritis. He had had no pneumonia, no pleurisy and no tonsillitis. He suffered from chronic indigestion,

dry mouth and constipation. He had some fluttering of the heart years before admission, and a chancre seventeen years before. The patient was of a nervous disposition and inclined to worry.

Fluoroscopic examination, Sept 20, 1916, showed no marked enlargement of the heart. The upper portion of the mediastinum showed a pulsating shadow that extended about 3 cm outside the right and the left sternal margins. This shadow was pulsating, which is quite characteristic of an aneurysm. Both apexes were cloudy, especially the right, probably owing to the enlargement of the heart back of the aorta. The diaphragmatic movements were normal and there were a few pleural adhesions. The impression was that the patient had a sacculated aneurysm of the transverse arch.

Sept 15, 1916, the urine was clear and acid, with a specific gravity of 1.007, there were no albumin, sugar or casts. The Wassermann reaction was negative.

Dr J H Pleasants, who first saw the patient, Jan 9, 1924, considered it to be an instance of coarctation of the aorta similar to case 2, and called Dr W T Longcope into consultation. Dr Longcope reported that the marked features of the case were the comfort of the patient, who had rather deep, dusky lips and ears, and the extraordinary arterial pulsations above and below the clavicles and in the episternal notch. The pulsations that were below were in the infraclavicular

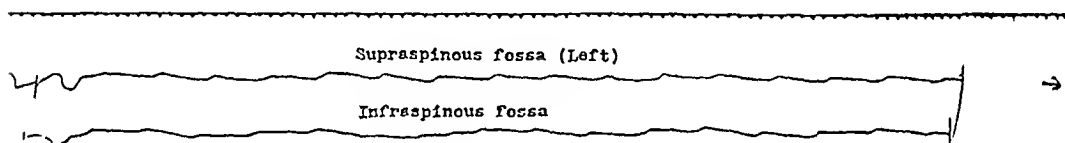


Fig 4 (case 2) —Pulsation in left interscapular area, these simultaneous tracings show that the pulsation occurs in the supraspinous fossa slightly before it reaches the infraspinous fossa, indicating that the pulsation is progressive from above downward.

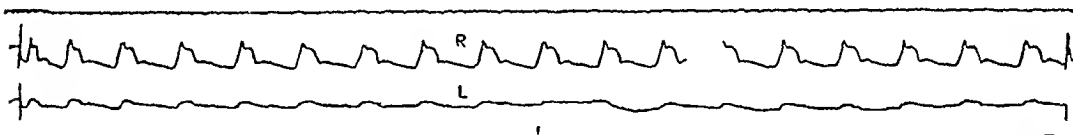


Fig 5 (case 2) —Simultaneous tracings from two radial pulses, the pulse waves reach the wrist simultaneously but the peak of the wave is delayed in the left radial as compared with the right. These observations bear out those of Stursberg²¹ (The difference in amplitude in the two radial pulses is due to difference in the recording apparatus leading from the two wrists. a similar delay in the peak of the left radial pulse wave occurred when the recording apparatus in the two arms was reversed.)

fossae. There were fairly well marked pulsation in the axillary artery, extraordinary visible pulsation in the upper portion of the back beneath the supraspinous muscles, and tortuous pulsating arteries beneath the angles of the scapulae. These pulsating vessels in the suprascapular regions could be felt like tortuous cords, and similar ones ran horizontally (more or less) from the angles of the scapula. The pulsations in the supraspinous muscles felt superficial and were felt well on deep pressure, when they elevated the wrist. On the right side pulsations extended up into the posterior cervical region. In the lower portion of the axilla were other tortuous pulsating arteries. The retromanubrial dulness was 5 cm to the right and 3 cm to the left in the third interspace. The maximum impulse in the fifth space was 11 cm from the midline. It is particularly noteworthy that with peripheral pulsations there was practically no pulsation beneath the manubrium. The apical impulse was forceful, and the marked tracheal tug was visible. There was a difference between the radial pulses, the one on the

right being more marked. At the apex there was a dull first sound accompanied by a systolic murmur. The second sound was completely obliterated by a high pitched diastolic sound. This double murmur was heard all over the heart, the diastolic being particularly loud along the left sternal border, and heard also at the aortic border. The second sound was not heard anywhere. The first sound was not loud. Over the pulsating area in the back and beneath the clavicles there was a systolic bruit, loudest on the right. In the left supraspinous region was a soft diastolic murmur. The physical signs were those of aortic insufficiency with an enlargement of the left side of the heart and of the aorta, combined with a remarkable peripheral anastomotic arterial condition over the chest which strongly suggested coarctation of the aorta. The fact that the fluoroscope showed only slight enlargement of the aorta supports this view. The murmur might be associated with patent ductus botalli.

Fluoroscopic examination showed a moderate grade of dilatation of the transverse arch of the aorta, probably aneurysm. Unfortunately, this patient left the city and it was impossible to study his condition more thoroughly.

While there were no blood pressure determinations in this case, a difference in size of the radial pulses was noted by two observers, the right pulse being larger than the left.

The case presents practically the same signs as were found in case 2, again with aortic insufficiency. The clinical diagnosis of aneurysm had been made in this case as it had in case 1 before the true condition was recognized.

CASE 4—*Coarctation of the aorta, Streptococcus viridans septicemia, with recovery*

A negress entered Johns Hopkins Hospital, Feb 3, 1925, complaining of weakness and an "awful feeling" in the mouth. She had had nocturia since childhood and one attack of dyspnea and palpitation. There were marked pulsations in the upper extremities and in areas described in the back. A loud systolic bruit was heard in the interscapular area. Feeble pulsation in the lower extremities and high pulse pressure in the arms were noted.

The father died at 80 of old age, the mother died at 45, of an unknown cause. The patient had five sibs, three of whom died in infancy of unknown causes and one at 28 of an unknown cause. One sister and one son were living and well. There was no history of tuberculosis, renal or cardiac disease, cancer, nervous diseases or insanity.

The patient's health had always been good, she had the usual childhood diseases and had pneumonia as a girl. She was operated on in Johns Hopkins Hospital in 1919, a myomectomy being performed, she had postoperative pneumonia. She had had no diphtheria, typhoid, malaria, influenza, scarlet or rheumatic fever or chorea. She was not subject to headache, dizziness or fainting, and had no feeling of fulness in the head, she wore glasses, had rare sore throat, no diplopia, no scotoma, and the nose and ears were negative. The patient had some cardiac palpitation and dyspnea in 1919, both gradually disappeared after the myomectomy. She had no hemoptysis, no chronic cough and no edema. The appetite and the digestion were good, and the bowels were regular. She had had hemorrhoids without symptoms for many years, but no hematemesis, melena or jaundice. The menses began at 16, were regular, of a duration of four or five days, but had ceased with the operation (1919). She had had nocturia once since childhood, but no urinary disturbances. She said she had no genital lesion, and had no symptoms of syphilis. She had acute arthritis of both knees four years before admission, but the joints were neither hot nor very tender. She used alcohol occasionally, but no drug or tobacco.

For four weeks she had had fever, ushered in by a sense of chilliness, which had not returned. She had grown very weak, had no appetite, and had also become somewhat short of breath. The urinary output had decreased, and she felt some urethral burning.

The report of a physical examination by Dr C S Keefer was that the patient seemed comfortable at rest, and had no dyspnea. Examination of the head revealed nothing abnormal, there were no petechiae, but there were numerous

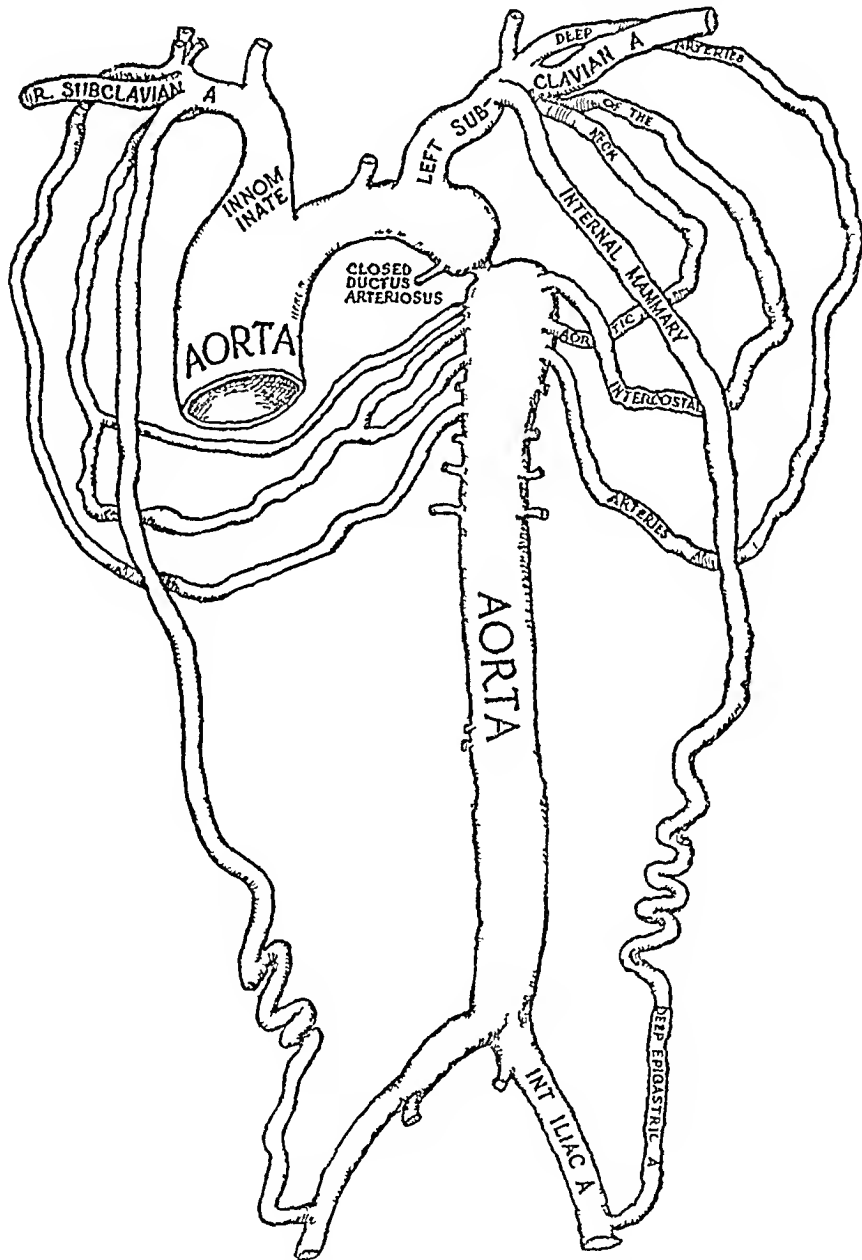


Fig 6 (after Walshe, from Abbott and Dawson) —Coarctation of the aorta (This is not drawn to scale, during life the dorsal scapular arteries, included here among the "deep arteries of the neck," are much larger than indicated)

cherry angiomas over the skin of the chest and back. In the episternal notch, in the carotids and below the clavicles and brachials there was marked visible pulsation. The pulse was bounding and collapsing in type, one could feel this pulsation quite definitely. There did not seem to be a difference in the two arms on palpation. There was no tracheal tug and no general glandular enlargement. The lungs were clear.

The heart was somewhat enlarged. The point of maximum impulse was in the fifth space, just outside the nipple line. No thrills were felt and no shocks. In the back, at the angle of the scapula, just below the infrascapular space there was a definite pulsation on both sides, which felt like a dilated artery on each side. The intercostal arteries could be felt to pulsate in the second and third interspaces anteriorly, as far out as 5 cm. from the midsternal line. The intercostal artery could be felt to pulsate in the second interspace. At the apex the sounds were well heard. There was a distinct systolic murmur, which did not seem to be transmitted from the mitral area but rather from above. Over the base, extending to the right and the left of the sternum and to the episternal notch, there was a loud systolic murmur, it was rough and was followed by a loud second aortic sound. This murmur was louder to the left of the sternum than to the right, and there was a slight increase in retromanubrial dullness. No thrill was felt. In the interscapular space there were loud systolic bruits over the areas in which pulsation has been described in the foregoing. The abdomen was negative. The pulsation in the legs was feeble.

On these data Dr. Keefer felt that the patient had coarctation of the aorta.

The red blood cells totaled 4,088,000, leukocytes, 8,600, hemoglobin, 53 per cent, and the color index was 0.65 per cent. The differential count was polymorphonuclear neutrophils, 78 per cent, small lymphocytes, 12 per cent, large mononuclears, 5 per cent, and transitionals, 5 per cent.

February 5, an electrocardiogram gave a rate of 80, a sino-auricular rhythm, P-R interval, 0.18 second, and wave T diphasic in Leads I and II. The diagnosis was a normal mechanism, with the levogram predominant.

February 6, the patient was seen by Dr. W. T. Longcope, who concurred in the diagnosis of coarctation of the aorta. The stool was normal, Widal tests and the Wassermann reaction were negative.

A teleroentgenogram of the heart, made by Dr. F. H. Baetjer, February 5, showed the maximum shadow to the right 4 cm., and to the left 9 cm. The heart was normal. There was a localized dilatation of the arch of the descending aorta, which might involve the subclavian artery.

The blood pressure, both systolic and diastolic, tended to be higher in the left than in the right arm, the reverse of the findings in cases 1 and 2. The figures were as follows: left arm (systolic), 173-230, right arm, 168-210, left arm (diastolic), 85-120, right arm, 80-107, left leg (systolic), 120-150, right leg, 140-162, left leg (diastolic), 72-110, right leg, 75-110.

February 7, *Streptococcus viridans* had been cultivated from the blood. Blood cultures showed this organism to be present in the blood on several occasions, and at discharge, March 30, 1925. The urine was cloudy, with a specific gravity of from 1.006 to 1.032, sugar, 0, albumin, always present, almost constant casts, occasional red cells in the sediment, frequent leukocytes.

June 6, 1924, the patient returned to the outpatient department by request. The blood culture was negative. The patient felt well and had gained in weight. The patient had continued well. In this report we are interested only in the condition of stenosis of the aorta, the case is also of unusual interest because of the *Streptococcus viridans* septicemia, and will probably be reported more fully from that point of view.

COMMENT

Pathologic Anatomy—The stenosis in the cases under consideration is described as symmetrical and annular, and the portion of aorta involved as rigid. The grade of stricture varies up to complete obliteration (described above). In our series, cases 1 and 4 may be supposed to have a moderate grade of localized coarctation or a fusiform narrowness of the whole isthmus, cases 2 and 3, because of the highly developed collateral circulation, are probably well developed instances

of a sharp stenosis or complete obliteration of the aorta near the entrance of the ductus botalli

Pathologic Physiology—This can perhaps be shown best by a diagram prepared by Abbott and Dawson,¹² from Walshe's¹³ time honored description. From the clinical standpoint, the most important vessels by far are the dorsal scapular arteries. The circulation in the intercostal arteries from the aorta is reversed, as is that in the deep (inferior) epigastric arteries. There is no necessary cyanosis.

Sex—The recorded cases show that a majority of instances of coarctation occur in men, but it is not true, as stated by some writers, that the condition is limited to males. Cases in women are reported by Kohn,¹⁴ Weber,¹⁵ Lommel,¹⁶ Focken,¹⁷ Gossage¹⁸ and others. Case 4 of our series was in a woman.

Race—I have seen no reports of cases in the brown or yellow race, but there is at least one case already on record that occurred in a negro.¹⁹ Case 4 of our series was in a negress. In case 1 the patient was born in Italy. In cases 2 and 3 the patients were born in this country, in case 2 the patient obviously was of Teutonic extraction, and in case 3 presumably so.

Age—The condition occurs at any age after birth, but it has not been observed in the embryo. The "critical" ages are in early infancy and in the third decade, many patients die during the first critical period, when the collateral circulation is becoming established, while others die in early adult life from myocardial strain. If the patient survives this second strain, he seems to do well. One patient with coarctation lived to be 92 years of age. The ages of our four patients were 35, 58, 54 and 40.

Occupation—The condition is compatible in some cases with hard labor, patient 1 of our series did hard labor on the street railway, but was forced to take periods of rest. Patient 2 has always worked as a

12 Abbott, M. E., and Dawson, W. T. The Clinical Classification of Congenital Cardiac Disease, *Internat. Clin.* **4** 156, 1924.

13 Walshe, W. H. Case of Presumed Quasicongenital Coarctation of the Arch of the Aorta, *M. Times & Hosp. Gaz.* **36** 389, 1857.

14 Kohn, A. A Case of Dilatation of the Aorta Due to Constriction at the Isthmus, *M. Rec.* **79** 652, 1911.

15 Weber, R. P., and Price, F. W. Coarctation of the Aorta in an Adult, with Death Due to the Rupture of an Aneurysm in the Neck, *Lancet* **2** 692, 1912.

16 Lommel, F. Ueber Stenose des Aortenisthmus, *Med. Klin.* **15** 892, 1919.

17 Focken, Ernst. Isthmusstenose der Aorta und Septische Endokarditis, *Ztschr. f. klin. Med.* **100** 179 (May) 1924.

18 Gossage, A. M. Coarctation of the Aorta, *Proc. Roy. Soc. Med. (Clin. Section)* **2** 210, 1909.

19 Weidman, F. D. Congenital Stenosis (Coarctation) of the Isthmus of Aorta, *Proc. Path. Soc. Philadelphia* **16** 78, 1914.

laborei, and is still able to do his share of hard work. Patient 3 is listed as a machinist, while patient 4 is a housewife. Patients with this condition are thought not to be fit for general military service owing to their liability to myocardial insufficiency.

History—We have not found a history of physical insufficiency in childhood in any of our cases. A history of periods of palpitation of the heart was obtained in each of our cases, and three gave a history of definite phases of dyspnea.

Nocturia is a common and, we believe, an important symptom, especially as it usually occurs without evidence of nephritis. No note is found in one case (case 3) as to its presence or absence, but in each of the other three cases it has occurred since childhood, or as long as the patient can remember. It is probably related in some way to the vascular abnormalities and changes in blood pressure.

Symptoms—The symptoms in most cases are those of myocardial insufficiency—dyspnea, palpitation, edema, etc. Occasionally intermittent claudication occurs (as in case 1), but this is a rare symptom. One of our patients (patient 2) complains of severe cramps in the legs "on stretching" himself in bed in the morning, the cramps occur regularly and cause him to walk about the room to get relief. There may be pain in the interscapular region from the dilated dorsal scapular artery, this symptom called attention to the pulsation and made the diagnosis possible in case 2. In this case the pain occurred only as a result of work.

Signs—Bilateral pulsation in the interscapular region was present in all four cases. It called attention to the presence of coarctation of the aorta in three cases, possibly also in the fourth. In two cases (cases 1 and 4) this pulsation constituted the outstanding physical sign, and the condition would probably have been overlooked but for its presence. Collateral circulation through the dorsal scapular arteries, carrying arterial blood downward from the deep arteries of the neck into the intercostal arteries and through them into the aorta, causes this bilateral pulsation. Further collateral circulation was well established in cases 2 and 3. The pulsation was clearly visible, as well as palpable, in cases 1, 2 and 3, but in case 4 it was only palpable. A systolic murmur was heard in each case over the areas of pulsation in the back.

Collateral circulation was established in cases 2 and 3 through superficial pulsating arteries in the axillae and subscapular regions, the flow being obliquely from above downward into the intercostal arteries and into the aorta (fig 3). These arteries presumably drained part of the system of deep arteries of the neck (fig 6). In case 4 the pulsations of certain intercostal arteries were palpable, indicating that they were probably carrying blood by collateral circuits. An interesting phenomenon is observed when these arteries are stripped of blood by pressure

on release of pressure, blood enters the artery from either end, but there is pulsation only when the upper end of the artery is patent

Systolic murmurs seem to be present constantly over arteries carrying blood by collateral channels. A systolic murmur may be present over the whole extent of the thoracic and lumbar aorta (case 2)

Aortic insufficiency, with characteristic secondary changes in the heart, was present in two of our four cases (cases 2 and 3). It is commonly associated with coarctation of the aorta¹. The lesion of the aortic valves apparently is of neither rheumatic nor syphilitic etiology. Recognized congenital abnormalities of the aortic valves without insufficiency have been noted postmortem. Le Count²⁰ believes that the aortic valve lesions are probably indications of repair thrombosis and organization of minute ruptures of the aortic leaflets, the result of increased arterial pressure.

Discrepancy between the degree of apparent and palpable pulsation in the upper extremities and that of the legs and abdominal aorta is very striking. This is especially true in cases with associated aortic insufficiency, but there is a definite increase in the visible pulsation of all the arteries of the upper part of the body, even in those patients who have no associated aortic insufficiency. The radial pulse is vigorous and bounding but not collapsing, unless there is associated aortic insufficiency. Pulsation in the brachial, axillary, subclavian and carotid arteries is increased, that in the abdominal aorta and in the arteries of the legs much diminished.

Blood pressure determinations are bizarre. In cases 1 and 2 the blood pressure was consistently higher in the right brachial artery than in the left. We have no records of this feature in case 3. In case 4 the systolic and diastolic blood pressures tended to be slightly higher in the left arm than in the right, though on one occasion it was higher in the right, the discrepancy of pressure readings in case 4 is hardly marked enough or constant enough to be important. The blood pressure in the legs was much lower than that in the arms in all cases in which it was noted (cases 1, 2 and 4).

Difference in the size of the radial pulses was noted in cases 2 and 3, in each of these the right radial pulse seemed larger to the palpating finger. In cases 1 and 4 the radial pulses were noted as being of equal size. Several previous case reports have shown the right radial pulse to be larger than the left²¹. This difference (pulsus differens) has

20 Le Count. Occlusion of the Aortic Arch at the Isthmus, *Coarctation Aortae*, Tr. Chicago Path. Soc. **9** 88, 1914.

21 Brown, Alexander. Congenital Stenosis of the Aorta, *Lancet*, **1** 1719, 1912. Ermann, F. Ein Fall von Angeborener Stenose der Aorta an der Einknickungsstelle des Ductus Botalli, *Berl. klin. Wchnschr.* **10** 217, 1873. Stursberg, H. Sphymographische Befunde bei Verengerung der Aorta am Isthmus, *Deutsches Arch. f. klin. Med.* **107** 33-38, 1912. Schickhold, P. Die Verengerungen der Aorta in der Gegend des Ductus Botalli, *München med. Wchnschr.* **44** 1279, 1897.

been well studied and reported in previous cases of coarctation²² These authors found that there was no actual delay of the ascending limb of the radial pulse in the left arm as compared with that in the right, but that the apex of the pulse wave was blunt and retarded in the left radial, as compared with the right Their findings were comparable to those shown in figure 5 There is an actual delay in the femoral pulse as compared with the radial Pulsus differens in the radial arteries, due to delay and blunting of the apex of the left radial wave, has been demonstrated by von Ziemssen²³ in two cases in which plaques were found postmortem partly occluding the left subclavian artery Such a cause is, however, probably lacking in coarctation of the aorta, in the case of Ermann,²⁴ the orifices of the two subclavian arteries measured the same, in that of Schickhold,²⁵ in which the left radial pulse was smaller than the right by palpation, the orifice of the right subclavian artery measured 35 mm while that of the left measured 45 mm

No doubt the chief difference between the pulse at the two wrists is due to the relative delay of the apex of the left radial pulse wave and its rounded crest It is unlikely that there is any true difference in total blood supply to the two arms, since no obstruction of the left subclavian artery is found in these cases postmortem, and the pulse pressure in the two arms is not consistently higher in one than in the other arm

It is difficult to account for the demonstrated difference in form in the two radial pulse waves It is reasonable to suppose, however, that the proximity of the stenosis to the origin of the left subclavian artery may cause the difference, this is borne out by two considerations first, the left radial tracing is unusual, while the right radial tracing is of quite natural appearance, second, the obstruction at the isthmus would be likely to cause momentary slowing of the blood stream in the aorta, backward at least as far as the left subclavian artery Such slowing in the passage of blood past the mouth of the subclavian artery would produce the type of pulse tracing that is obtained from the left radial artery

In figure 4 is shown a tracing that helped to show that the pulsations in the interscapular region are progressive from above downward Such a tracing helps to rule out aneurysm

Roentgenograms are disappointing One sees a generalized dilatation, usually moderate, of the arch of the aorta Aneurysm usually is eliminated from the diagnostic possibilities by this method The site

22 Scheele Berl klin Wchnschr 7 32, 1870 Stursburg (Footnote 21, third reference)

23 Von Ziemssen Ueber den Pulsus und seine Bedeutung bei Erkrankungen des Aortenbogens, Deutsches Arch f klin Med 46 285, 1890

24 Ermann (Footnote 21, second reference)

25 Schickhold (Footnote 21, fourth reference)

of stenosis lies behind the heart, and is so closely flanked to the right by the vertebral column as to make it impossible to inspect this portion of the aorta satisfactorily. The chief value of the roentgen ray is the ruling out of aneurysm.

The electrocardiogram is not modified by stenosis of the aorta.

SUMMARY

1 In the four cases of stenosis of the isthmus (coarctation) of the aorta recognized during life reported, two were thought to be instances of slight stenosis, two of well marked stenosis or total obliteration of the aorta at about the site of the entrance of the ductus botalli.

2 Postmortem reports show that the condition is rarely recognized during life.

3 Coarctation occurs more often in males than in females, it occurs at any age after birth, and is compatible in some cases with long periods of hard physical work.

4 Symptoms that may occur are palpitation, dyspnea, myocardial insufficiency, nocturia, cramps in the legs and intermittent claudication.

5 The signs that may occur are

(a) Bilateral pulsation in the interscapular region. This is the most important physical sign, the pulsation progresses from above downward.

(b) Relatively greater pulsation in the upper extremities than in the lower.

(c) Pulsating, superficial, collateral arteries, coursing obliquely across the back of the thorax downward toward the spine. Dilated intercostal arteries.

(d) Relatively higher blood pressure in the arms than in the legs.

(e) Tendency to higher blood pressure in the right than in the left arm.

(f) Pulsus differens, due to the relative delay of the apex of the left radial pulse and rounding of its apex.

(g) Tendency for the right radial pulse to feel larger than the left.

(h) Systolic murmurs over areas of interscapular pulsation, over the collateral arteries, at times over the arch of the aorta anteriorly or over the whole aorta posteriorly.

BIBLIOGRAPHY

- 1 Graham, R. Case of Obstructed Aorta, *Med-Chir Tr*, London 5 287, 1814.
- 2 Farre, J. R. On Malformations of the Human Heart, London, Longman, 1814, p. 13.
- 3 Cooper, A. Case of Ligature on the Aorta, in *Surgical Essays* by A. Cooper and B. Travers, London, Cox and Sons, 1818, p. 111.

4 Otto, A W Eine Zerreissung der Aorta, wegen stellenweiser grosser Verengerung derselben, Neue seltene Beobachtungen zur Anatomie, Physiologie und Pathologie gehorig **2** 66, 1824, Berlin, August Rucker

5 Bertin, R J, and Bouillaud, J Traité des maladies du coeur, edited by J Bouillaud **48** 158, Paris, J-B Bailliere, 1824

6 Laennec, R T H L'auscultation mediate, etc **2** 686, 1826, Paris, Chaude

7 Meckel, A Verschlussung der Aorta am vierten Brustwirbel, Arch f Anat u Physiol, Leipzig, 1827, p 345

8 Pelletier, B Observations recueillies a la clinique de M Trouve, Arch gen de med **18** 205, 1828

9 Reynaud, A Observation d'une obliteration presque complete de l'aorte, suivie de quelques reflexions, et precedee de l'indication des faits analogues, consignés dans les auteurs, J hebdom de med, Paris **1** 161, 1828

10 Jordan, J A Case of Obliteration of the Aorta, North of England M & S J, London **1** 101, 1830

11 Nixon, R L Case of Constriction of the Aorta with Disease of the Valves, Dublin J M Sc **6** 386, 1832

12 Nixon, R L Case of Constriction of the Aorta, Dublin J M Sc **5** 386, 1834

13 Schlesinger Wehnschr f d ges Heilk, Berlin, August Hirschwald, 1835, p 489

14 Legrand Du retrecissement de l'aorte, Arch gen de med **8** 528, 1835

15 Barth, J P Des retrecissements et des obliterations spontanees de l'aorte, thesis, Paris, 1837, no 189

16 Maigne Note sur un cas de retrecissement de l'aorte et de l'artere sous-claviere gauche, Bull Soc anat de Paris **12** 219, 1837

17 Romer, A Einer vollstandige Verschlussung der Aorta bei einem 50 jahrigten Manne, Med Jahrb d k k Osterr-Staates, Vienna **29** 208, 1839

18 Mercier, A Retrecissements avec obliteration presque complete de la portion thoracique de l'aorte, Bull Soc anat de Paris **14** 158, 1839

19 Hargrave Stricture of the Aorta, Houston's Catalogue **2** 117, 1840, Dublin, Hodges and Smith

20 Andral Clinique med **3** 61, 1840

21 Craigie, D Instance of Obliteration of the Aorta, Beyond the Arch, Illustrated By Similar Cases and Observations, Edinburgh M & S J **56** 427, 1841

22 Wise, T A Congenital Closure of the Descending Aorta, Tr M & Phys Soc Calcutta **8** 384, 1842

23 Fletcher Med-Chir Tr, London **25** 282, 1842

24 Muriel, Wilham Case of Contracted Aorta, Guy's Hosp Rep **15** 453, 1842

25 Hamernjk, J Einige Bemerkungen uber die obliteration des Anfangsstuckes der absteigenden Aorta, Vrtljschr f d prakt Heilk, Prague **1** 41, 1844

26 Tiedemann, F Von der Verengerung und Schliessung der Pulsadern in Krankheiten, Heidelberg, 1843, p 15 (Pockels-Hensinger)

27 Chevers, N Permanence of the Ductus Arteriosus and Constriction of the Thoracic Aorta, London M Gaz **36** 187, 1845

28 Bochdalek Obliteration der Aorta, Vrtljschr f d prakt Heilk, Prague **4** 160, 1845

29 Smith, E Premature Occlusion of the Foramen Ovale, Proc Path Soc London **1** 52, 1846

30 Crisp, E Diseases of the Blood Vessels, London, J Churchill, 1847, p 31

31 Babington, W Cyanosis Dependent on Patent Ductus Arteriosus with Disease of the Aortic Valves, Proc Path Soc London **1** 55, 1847

32 Rees, G A The Heart of a Child Presenting an Open State of the Ductus Arteriosus, Proc Path Soc London **2** 203, 1847

- 33 Dubrueil, J M Des anomalies artérielles, Paris, J B Balliere et fils, 1847, case 1, p 199
- 34 Von Loebel, G Zur Genese der Obliteration der Aorta an der Einmündung des Ductus arteriosus Botalli, Constatt's Jahresbericht **2** 192, 1848
- 35 Blakiston, P Diseases of the Chest, Philadelphia, Lea and Blanchard, 1848, p 157
- 36 Hamernjk, J Vrtljschr f d prakt Heilk, Prague, 1848, p 40
- 37 Oppolzer Obliteration der Aorta, Vrtljschr f d prakt Heilk, Prague **19** 69, 1848
- 38 Gutherez Die Obliteration der Aorta, N med-chiu Ztg, Munchen **3** 193, 1849
- 39 Van Leeuwen, D H Over de Diagnose van Aangeboren Vernauwingen Sluiting der Aorta, Nederl-Lancet **5** 65, 1849
- 40 Lebert, H Ueber die Verengerung der Aorta in der Gegend des Ductus arteriosus, Virchows Arch f path Anat **4** 327, 1852
- 41 Cruveilhier, J Traité d'anat pathol gen Paris **2** 313, 1852, Paris, J B Balliere et fils
- 42 Rokitsansky, K Bevorstehende vollständige Obliteration unterhalb der Einmündung des Ductus Arteriosus-Lungenodem Insufficienz der Aortenklappen, p 58, Obliteration der Aorta überhalb der Insertion der Exsudat linker Seite, p 59, Krankheiten der Arterien, 1852, Vienna, Wichtigsten
- 43 Harlin Stricture der Aorta, Virchows Arch f path Anat **5** 273, 1853
- 44 Rokitsansky, C Académie des sciences de Vienne, 1853
- 45 Schmidt, F J J Krankheiten des Herzens und der Grossen Gefasse, Constatt's Jahresbericht **2** 58, 1853
- 46 Willigk, A Angeborene Enge des Arcus Aortae, Vrtljschr f d prakt Heilk, Prague **38** 19, 1853
- 47 Dlauhy Rokitsansky's Lehrb der path Anat **4** 232, 1855
- 48 Harrison, T J Singular Abnormality of the Arterial System, Constriction and Obliteration of the Aorta, Penins J M, Ann Arbor, Mich **3** 514, 1855
- 49 Rokitsansky, C Lehrbuch der path Anat **2** 337, 1856, Wilhelm Braumüller
- 50 Peacock, T B Contraction of the Pulmonary Orifice and Artery, with Imperfection of the Septum of the Ventricles and Absence of the Ductus Arteriosus, Tr Path Soc London **7** 83, 1856
- 51 Virchow, R Gas Abhandl z wissensch Med, Frankfurt, 1856, p 416
- 52 Oppolzer Obliteratio Aortae incompleta congenita, Allg Wien med Ztg **1** 53, 1856
- 53 Jones, S Case of Complete Obliteration of the Thoracic Aorta, Tr Path Soc London **8** 159, 1857
- 54 Dumontpallier Du retrecissement aortique au niveau de l'abouchement du canal arteriel, Gaz med de Paris **12** 52, 188, 295, 1857
- 55 Rosenstem, S Virchows Arch f path Anat **12** 286, 1857
- 56 Viaud-Grandmarais Double retrecissement dont l'un congenital, de la crosse de l'aorte, dilatation sacciforme, Bull Soc anat de Paris **32** 417, 1857
- 57 Bamberger, H Lehrbuch der Krankheiten des Herzens, W Braumüller, 1857, p 446
- 58 Houel, C Manuel anat path, Paris, 1857, p 471, Paris, J B Balliere et fils
- 59 Beraud-Jordan Obliteration de l'aorte, Compt rend Soc de biol **4** 177, 1857
- 60 Leudet, E Recherches anatomiques et cliniques sur le rétrécissement de l'aorte au niveau du canal artériel, Gaz med de Paris **13** 44, 1858
- 61 Jones, J Obliteration der Brustaorta, Schmidt's Jahrbuch, Leipzig **98** 290, 1858
- 62 Kjellberg Hygiea medicinsk **21** 376, 1859

- 63 Wood Obliteration of the Aorta, London M Times & Gaz **39** 172, 1859
- 64 Wilks Communication Between the Pulmonary Artery and Aorta, Tr Path Soc London **11** 57, 1860
- 65 Barker, T A Case of Imperforate Arch of the Aorta, Med-Chir Tr, London **43** 131, 1860
- 66 Rauchfuss, C Ein Fall von Stenose der Aorta an der Einmündungsstelle des Ductus arteriosus bei einem drei wochentlichen kinde, Virchows Arch f path Anat **18** 544, 1860
- 67 Peacock, T B On Contraction and Obliteration of the Aorta Near the Junction of the Ductus Arteriosus, British and Foreign Med-Chir Rev, New York **25** 341, 1860
- 68 Mann Ein Fall von Stenosis aortae descendens, Deutsch Klinik **13** 118, 1861
- 69 Rokitansky, C Krankheiten der Arterien, 1862, observation 21
- 70 Almagro, M Persistance du canal arteriel, thesis, Paris, 1862, no 63, p 57
- 71 Scheiber, S H Ueber einen Fall von Obliteration der Aorta entsprechend dem Ductus arteriosus Botalli, Virchows Arch f path Anat **26** 218, 1863
- 72 Forster, A Handb der path Anat, 1863, p 726, Leipzig, Voss
- 73 De Barry, J Verengerung der Aorta an der Einmündungsstelle des Ductus Botalli, Virchows Arch f path Anat **31** 434, 1864
- 74 Degen Persistenz des Isthmus aortae, Tod durch Ruptur der Aorta, Deutsches Arch f klin Med **3** 614, 1867
- 75 Quinquad Insuffisance aortique retrecissement congenital de l'aorte, Mort subite, Bull Soc anat de Paris **43** 209, 1868
- 76 O'Flaherty Ein Fall von Stenocardie und Stricture der Aorta, Jahresb u d Leistung d ges Med **2** 71, 1868
- 77 Pommier Retrecissement de l'aorte à l'union de la crosse avec la portion descendante, Bull Soc anat de Paris **44** 37, 1869
- 78 Louville, H Anomalie des valvules de l'aorte, Compt rend Soc de biol **21** 129, 1869
- 79 Wrany, A Der Ductus arteriosus Botalli, in seinen physiologischen und pathologischen Verhältnissen, Oesterr Jahrb f Paediat, Vienna **1** 1 1871
- 80 Bradley, S M Note on a Peculiar Origin of the Right Subclavian Artery, J Anat & Physiol **5** 341, 1871
- 81 Eppinger, H Stenosis Aortae Congenita seu Isthmus Persistens, Vrtljschr f d prakt Heilk, Prague **112** 31, 1871
- 82 Traube and Hertel, I Ein Fall von angeborener Aortenstenose, Berl klin Wchnschr **8** 337, 1871
- 83 Skoda, J Case of Probable Partial Obliteration of the Aorta, Lancet **2** 13, 1871
- 84 King, R Malformation of the Heart, Tr Path Soc London **23** 83, 1872
- 85 Riegel, F Ueber regelwidrige Enge des Aortensystems, Berl klin Wchnschr **9** 465, 479, 1872
- 86 Purser, J M Narrowed Aorta, Disease of Mitral Valve, Dublin J M Sc **56** 466, 1873
- 87 Redenbacher, W Verengerung der Aorta descendens an der Insertionsstelle des Ductus Botalli, Aertzl Int-BI, Munchen **20** 97, 1873
- 88 Moutard-Martin Retrecissement congenital de l'aorte, atherome, hypertrophie du coeur, absence d'une des valvules sigmoïdes, Bull Soc anat de Paris **49** 737, 1874
- 89 Moutard-Martin and Rendu Des retrecissements congenitaux de l'aorte, Bull Soc anat de Paris **49** 888, 1874
- 91 Taruffi Memoria della Societa Medico-Chirurgica di Bologna **8** 194, 1875
- 92 Moore, N Two Examples of Malformation of the Heart, St Bartholomew's Hosp Rep **11** 225, 1875

- 93 Goodhart, J F Coarctation of the Aorta Below Left Subclavian, Tr Path Soc London **26** 68, 1875
- 94 Moutard-Martin Rétrécissement congénital de l'aorte, Bull Soc anat de Paris **1** 521, 1876
- 95 Moore, N Examples of Malformations of the Heart, St Bartholomew's Hosp Rep **12** 101, 1876
- 96 Luttich Fall von Obliteration der Aorta in der Gegend des Ductus Botalli, Arch d Heilk, Leipzig **17** 70, 1876
- 97 Waggaman Congenital Stenosis of the Aorta, Tr M Soc District of Columbia **3** 65, 1876
- 98 Barlow, T Congenital Heart Disease, Two Cases, Tr Path Soc London **27** 140, 1876
- 99 Hornung, J Obliteration der Aorta, Wien med Wchnschr **16** 369, 1876
- 100 Quincke, H Cyclopaedia of the Practice of Medicine, edited by Dr H von Ziemssen, English translation, New York, William Wood & Co **6** 473, 1876
- 101 Lockwood, C B Obliteration of the Arch of the Aorta at the Level of the Ductus Arteriosus, St Bartholomew's Hosp Rep **14** 352, 1878
- 102 Legg, J W Obliteration of the Aorta, Tr Path Soc London **29** 65, 1878
- 103 Kriegk, M Drei neue Falle von Stenose der Aorta in der Gegend der Insertion des Ductus Botalli, Vrtljschr f d prakt Heilk, Prague **137** 47, 1878
- 104 Lancereaux, E Traité d'anatomie pathologique **2** 837, 1879-1881
- 105 Finlay, D W Malformation of the Heart, Stenosis of the Pulmonary Valve, Tr Path Soc London **30** 262, 1879
- 106 Chiari, H Ueber ein Cor triloculare, Jahrb f Kinderh, Leipzig, **4** 219, 1879
- 107 Osler, W Cases of Cardiac Abnormalities, Montreal Gen Hosp Rep **1** 177, 1880
- 108 Lees, D Case of Malformation of the Heart, Tr Path Soc London **31** 58, 1880
- 109 MacKenzie, S Case of Congenital Malformation of the Heart, Tr Path Soc London **31** 66, 1880
- 110 Knerim, H P Ein Fall von Stenosis der Aorta in der Gegend der Insertion des Ligamentum arteriosum, Marburg, 1880
- 111 Barié, E, and DuCastel, R Etude clinique sur les embolies de l'aorte et recherches experimentales sur la production des souffles cardiaques, Arch gén de med **147** 29, 1881
- 112 Armet, S Sur un cas d'oblitération par thrombus de l'aorte descendante, etude sur les effets de la ligature de l'aorte thoracique, thesis, Paris, 1881, no 389
- 113 Lesseliers, L Cas remarquable de rétrécissement de la crosse de l'aorte, Ann Soc de med de Gand **60** 45, 1882
- 114 Sommerbrodt, M Typischer Fall von volliger obliteration der Aorta thoracica an der Einmündungsstelle der Ductus Arteriosus, Tod in 46 Lebensjahre, Deutsche mil-arztl Ztschr, Berlin **12** 55, 1883
- 115 Holt, L E Malformation of the Heart, etc, New York M J **39** 335, 1884
- 116 Manneberg, I Ueber die Stenose und Obliteration der Aorta in der Gegend, etc, Breslau thesis, 1884
- 117 White, H An Example of the Remarkable Condition Described as Obliteration of the Thoracic Aorta, Lancet **2** 826, 1884
- 118 White, H Coarctation of the Aorta, Brit M J **2** 909, 1884
- 119 White, W H A Case of Coarctation of the Aorta, Tr Path Soc London **36** 178, 1885
- 120 Camecasse, M Retrécissement congénital de l'aorte, dilatation et hypertrophie du coeur, asystolie, Progres med **13** 422, 1885
- 121 Epstein, A Persistenz des Isthmus aortae und des Ductus arteriosus, Ztschr f Heilk **7** 293, 1886

- 122 Barie, E Du retrecissement congenital de l'aorte descendante, *Rev de med*, Paris **6** 343, 409, 501, 1886
- 123 Hofsten, S Fall af Aortastenos, *Hygiea*, Stockholm **48** 19, 1886
- 124 Crespin Un cas presenté a la Societe anatomique, dans la seance du 29 janvier, 1886, *Bull Soc anat de Paris* **61** 80, 1886
- 125 Alezais and Gilly Retrecissement congenital de l'aorte descendante, *Marseille med* **24** 594, 1887
- 126 Von Bamberger Obliteration der Aorta, *Wien med Presse* **28** 71, 1887
- 127 Paltauf, A Obliteration der Aorta, *Wien med Presse* **28** 71, 1887
- 128 Kundrat Obliteration der Aorta, *Wien med Presse* **28** 71, 1887
- 129 Loriga, G Stenosi ed Obliterazione congenita dell'aorta, *Riv clin di Bologna* **7** 529, 1887
- 130 Habershon, S H Congenital Malformation of Heart and Kidneys, Obliteration of Pulmonary Artery, *Tr Path Soc London* **39** 71, 1888
- 131 Fraentzel, O Ueber angeborene Enge in Aortensystem, *Deutsche med Wchnschr* **14** 589, 1888
- 132 Martens, G Zwei Falle von Aorten-Atresie, *Greifswald, J Abel*, 1889
- 133 Von Decker, A Zwei Falle von Isthmus aortae persistens, *Konigsberg, M Liedtke*, 1890
- 134 Hochsinger, C Ein Fall von congenitaler Aorten Stenose, *Wien med Presse* **31** 9, 1890
- 135 Laboulene, A, and Claisse, P Retrecissement congenital de l'aorte descendante a sa partie superieure, vers l'abouchement du canal arteriel, *Bull et mem Soc med d hop de Paris* **7** 945, 1890
- 136 Preisz, H Theilweise Obliteration des Aortenbogens und zwei Defecte in der Kammerscheidewand eines Herzens, *Jahrb f Kinderh*, Leipzig **33** 40, 1892,
- 137 Potain and Bureau Retrecissement congenital de l'aorte, *Gaz Hebdom de med*, Paris **29** 292, 1892
- 138 Witthauer, K Beitrag zu den Ursachen der Aortenstenose, *Deutsche med Wchnschr* **18** 788, 1892
- 139 Steiner, R Stenose der Aorta an der Insertionsstelle des Ductus Botalli, *Jahrb d Wien k k Krankenanst* **2** 715, 1893
- 140 Carmichael, J Congenital Heart Disease—Patent Ductus Arteriosus—Mitral Stenosis, *Edinburgh Hosp Rep* **2** 298, 1894
- 141 Claessen Casuistischer Beitrag zur Lehre von der Stenose des Isthmus aortae, *Internat klin Rundschau*, Vienna **8** 113, 1894
- 142 Stuertz E Stenose und Obliteration der Aorta an der Einmundungsstelle des Ductus Botalli, inaugural dissertation, Berlin, 1894, Berlin, C Vogt's Buchdruckerei (E Ebering)
- 143 Ciaglinski, K Przypadek wrodzonego zuzewienia aorty (Case of Congenital Constriction of the Aorta), *Gaz lek Warsaw* **14** 740, 1894
- 144 Flint, T B A Case of Ulcerative Endocarditis Associated with Coarctation of the Aorta, *Lancet* **2** 777, 1895
- 145 Theremin, E Etudes sur les affections congenitales du coeur, Paris, Asselin and Houzeau, 1895
- 146 Kretz, R Ein seltener Fall von Stenose am Isthmus der Aorta, *Wien klin Wchnschr* **8** 24, 1895
- 147 Carpenter, G A Case of Coarctation of the Aorta—Tubercles in the Choroid, *Pediatrics*, New York **2** 330, 1896
- 148 Ferrand Insuffisance aortique avec dilatation de l'aorte consecutive a une stenose congenitale de la portion terminale de la crosse aortique, *Semaine med* **16** 381, 1896
- 149 Langwill, H G An Unusual Cardiac Case, *Scot M & S J*, Edinburgh **1** 723, 1897
- 150 Riche, P Anomalie de la crosse de l'aorte, *Bull Soc anat de Paris* **72** 221, 1897

- 151 Wadstern, E Ueber Stenose und Obliteration der Aorta an oder in der Nahe des Ductus Botalli, Dissertation, Lund, abstr Jahrsb über d Leistung d ges Med, Berlin **32** 163, 1898
- 152 Vierordt, H Die angeborenen Herzkrankheiten, Nothnagel's Specielle Pathologie und Therapie, Vienna, Alfred Holder **15** 166, 1898
- 153 Huchard, H Traite clinique des maladies du coeur et de l'aorte **2** 333, Octave Doin, 1899
- 154 Schlesinger, H Stenosis of the Aorta Near the Duct of Botalli, Internat Clin **4** 140, 1900
- 155 MacCallum, W G Congenital Malformations of the Heart, as Illustrated by the Specimens in the Pathological Museum of the Johns Hopkins Hospital, Bull Johns Hopkins Hosp **11** 69, 1900-1901
- 156 Bumke, O Ein Fall von Isthmusstenose mit Ruptur der aufsteigenden Aorta, inaugural dissertation, Kiel, 1901
- 157 Reicher, O Ein Fall von Isthmusstenose der Aorta, Allg Wien med Ztg **46** 268, 1901
- 158 Pic, A, and Bonnamour, S Un cas de retrecissement congenital de l'aorte thoracique chez un veillard atheromateux, Province med, Lyon **16** 554, 505, 1902
- 159 Reimtz, C Ueber congenitale Stenose und Obliteration am Isthmus aorta, inaugural dissertation, Kiel, 1902
- 160 Libman, E Congenital Stenosis of the Aorta at the Isthmus, Proc New York Path Soc **2** 20, 1902
- 161 Anders, J M Sudden Death in Aortic Stenosis with Report of Two Cases, One Complicated with an Aneurysmatic-Like Dilatation of the Aorta at Its Root, and Marked Stenosis of This Vessel Beyond the Dilatation, Med News **80** 872, 1902
- 162 Arloing, F Un cas probable de rétrécissement congenital de l'aorte descendante, Bull Soc méd hôp de Lyon **1** 295, 1902
- 163 Josefson, A Stenosis isthmus aortae, Hygiea, Stockholm **65** 131, 1903
- 164 Bonnet, L M Sur la lesion dite stenose congenitale de l'aorte dans la région de l'isthme, Rev de med, Paris **23** 108, 255, 335, 418, 481, 1903
- 165 Dick, G F Anomalous Fetus, Tr Chicago Path Soc **6** 131, 1904
- 166 Murray, G R A Case of Incomplete Coarctation of the Aorta, Necropsy, Practitioner, London, January-June, 1904, p 284
- 167 Vallette Un cas de retrecissement congenital de l'aorte, Marseille med **42** 765, 1905
- 168 Pansch, K C P Ueber Stenose des Isthmus Aortae mit gleich-zeitiger Persistenz des Ductus arteriosus Botalli bei Neugeborenen, inaugural dissertation, Giessen, 1905
- 169 Weigert, R Ueber einen Fall von angeborener Stenose der Aorta an der Einmündung des Ductus arteriosus Botalli, Allg med Centr-Ztg, Berlin **74** 1, 1905
- 170 Pappenheimer, A M Stenosis of the Aorta at the Juncture of the Isthmus, Proc New York Path Soc **5** 177, 1905-1906
- 171 Pappenheimer, A M A Case of Stenosis of the Arch of the Aorta, Proc New York Path Soc **6** 95, 1906
- 172 Vallette, P, and Mollaret, J Un cas de retrecissement congenital de l'aorte chez un nourrisson, Marseille med **43** 41, 1906
- 173 Kovesi, G Stenosis isthmus aortae, Orvosi hetil, Budapest **50** 1055, 1906
- 174 Santas, M A Estenosis congenita dell istmo de la aorta en un individuo de 61 anos, Rev Soc méd Argent, Buenos Aires **14** 17, 1906
- 175 Audry, J Retrecissement de l'isthmus de l'aorte chez un nouveau-ne, Lyon med **106** 161, 1906
- 176 Klotz, O The Closure of the Ductus Arteriosus and Its Bearing on Arteriosclerosis, Tr A Am Phys **22** 213, 1907

- 177 Carpenter, G A Case of Coarctation of the Aorta, Rep Soc Study Dis Child, London **2** 158, 1907-1908
- 178 Monckeberg Einige Komplikationen bei angeborener Stenose des Isthmus der Aorte, Verhandl d deutsch path Gesellsch **11** 267, 1908
- 179 Weinberger, M Weitere Beitrage zur Radiographie der Brustorgane, Med Klin **4** 584, 1908
- 180 Carpenter, G Defective Auricular Septum, Arch of Aorta Constricted at Its Junction with the Ductus Arteriosus, Rep Soc Study Dis Child, London **2** 34, 275, 1908-1909
- 181 Hochcinger, C Pfaundler and Schlossmann Diseases of Children **3** 474, Philadelphia, J B Lippincott & Co, 1908
- 182 Cautley, E Stenosis of the Isthmus Aortae, with Patent Ductus Arteriosus and Patent Interventricular Septum, Proc Roy Soc Med, London, Sect Study Dis Child **2** 34, 1908-1909
- 183 Strassner, H Ein Fall von volliger Obliteration der Aorta an der Einmündungsstelle des Ductus Botalli, Deutsches Arch f klin Med **95** 344, 1908
- 184 Humphrey, Allbutt, and Rolleston System of Medicine **6** 286, 1909, London, MacMillan & Co
- 185 Keith, A Malformations of the Heart, Lancet **2** 359, 1909
- 186 Oberndorfer, S Demonstration einer Aortenruptur bei kongenitaler Aortenstenose, Verhandl d deutsch path gesellsch **14** 345, 1910
- 187 Variot, G, and Roudinesco Retrecissement congenital de l'aorte, Bull Soc de pediat de Paris **12** 226, 1910
- 188 Borisova, A P Two Cases of Stricture of the Isthmus of the Aorta, Med Obozr, Moscow **74** 138, 1910
- 189 Sella, H Aortenruptur und Aortenaneurysma bei Aortenstenose am Isthmus, Beitr z path Anat u z allg Path, Jena **49** 501, 1910
- 190 French, H An Unusual Case of Aortic Disease, Probably Congenital Coarctation, Tr M Soc London **34** 426, 1911
- 191 Zenoni, C Occlusione Completa dell'Aorta Discendente, Arch per le sc med **35** 1, 1911
- 192 Van den Berg, H M Stenosis Isthmi Aortae, Nederl Tijdschr v Geneesk **2** 773, 1911
- 193 Marx, H Ueber einen Fall von zunehmender Stenose der Aorta vom Conus bis zur Einmündung in den Ductus Botalli, inaugural dissertation, Heidelberg, A K Boeminger, 1912
- 194 Moon, R O Case of Congenital Stenosis of the Aorta, Lancet **1** 1531, 1912
- 195 Gossage, A M Case of Coarctation of the Aorta, Proc Roy Soc Med, London, Clin Sect 1, **6**, 1912
- 196 Kocemba, J Ein Fall von Stenose am Isthmus Aortae, inaugural dissertation, Bonn, 1913, H Trapp
- 197 Fruhwald, V Beitrag bei Kenntnis der post-operativen Todesfalle bei abnormer Enge der Aorta, Deutsche med Wchnschr **39** 889, 1913
- 198 Hirschfelder, A Diseases of the Heart and Aorta, Philadelphia, J B Lippincott Company, 1913, p 546
- 199 Sankott, A Ueber einen eigenartigen Fall von Stenose des Isthmus Aortae, Anat Anz, Jena **48** 261, 1915
- 200 Koster and Forselius Case of Complete Stenosis of the Aorta, Hygiea, Stockholm **77** 935, 1915
- 201 Laubry, C, and Marre, L Etude clinique et graphique d'un cas de rétrécissement congenital de l'isthme de l'aorte, Bull et mem Soc med d hôp de Paris **40** 2237, 1916
- 202 Weller, C V Coarctation of the Aorta with Patent Ductus Arteriosus, Internat A M Mus Bull, 1916, p 115

- 203 Lommel, F Ueber angeborene Verengung und Verschlussung des Aortenisthmus, Munchen med Wchnschr **64** 190, 1917
- 204 Bergmann, H Angeborene Atresie des Isthmus Aortae kombiniert mit Mitral-Stenose bei einem funfeinhalbjährigen Kind, Arch f Kinderh Stuttgart **67** 44, 1919
- 205 West, G R A Case of Stenosis of the Aorta, M J Australia **2** 195, 1919
- 206 Pende, N Sulla diagnosi della stenosi congenita dell'aorta, Malat d cuore, Rome **4** 101, 1920
- 207 Moon, R O Congenital Stenosis of the Aorta, Lancet **1** 1315, 1920
- 208 Hart, C Ueber die totale Obliteration des Aortenisthmus, Med Klin **16** 1337, 1920
- 209 Edelmann, A Isthmusstenose, Wien med Wchnschr **70** 1847, 1920
- 210 Hoche, L, and Morlot, R Un cas de stenose congénitale de l'aorte chez un nouveau-né, Bull et mém Soc anat de Paris **91** 91, 1921
- 211 Morlot, R, and Vermelin, H Deux cas de stenose congenitale de l'aorte chez le nouveau-né, Compt rend Soc de biol **85** 1082, 1921
- 212 Assmann, H Die Röntgendiagnostik der inneren Erkrankungen, Leipzig, F C W Vogel, 1921, p 78
- 213 Loeper and Marchal, G Un cas d'imperméabilité congénitale de l'isthme aortique compliqué d'endocardite maligne, Bull et mem Soc med d hôp de Paris **46** 1190 (July 28) 1922
- 214 Edelmann, A, and Maron, R Die Isthmusstenose der Aorta und ihre Differential Diagnose, Wien Arch f inn Med **4** 1 (April) 1922
- 215 Lambert, R A Anomaly of the Heart and Aorta, Multiple Defects with Stenosis of the Aortic Arch and Pulmonary Artery Becoming Descending Aorta, Internat A M Mus Bull **8** 177, 1922
- 216 Goldblatt, H Report of a Case of Coarctation of the Aorta at the Isthmus, with Dilatation and Rupture of the Ascending Portion of the Arch, Internat A M Mus Bull **8** 184, 1922
- 217 Strassmann, G Der plotzliche Tod bei Stenose des Isthmus Aortae, Beitr z gerichtl Med **5** 91, 1922
- 218 Dietlen, H Herz und Gefasse im Rontgenbild, Leipzig, Johann Ambrosius Barth, 1923, p 227
- 219 Reifenstein, B W Two Cases of Mycotic Aneurysm, Am J M Sc **168** 381 (Sept) 1924
- 220 Deneke, T Zur Klinik der Isthmusstenose der Aorta, Virchiows Arch f path Anat **254** 336, 1925
- 221 Bahn, K Über isolierte Dextrocardie mit Isthmusstenose der Aorta und Endocarditis lenta, Deutsches Arch f klin Med **146** 297 (March) 1925
- 222 Bruce, J W, and Ball, R Coarctation of the Aorta, Report of a Case, Am J Dis Child **31** 196 (Feb) 1926
- Note*—The foregoing references have all been consulted, with the exception of numbers 20, 44, 69, 170 and the two quoted below which are mentioned in the text
- Meckel, Johann Nachrichten der Acad d Wssensch, Berlin, 1755
- Wernicke, R Die Verengerung und Obliteration der Aorta in der Gegend des Ductus Arteriosus Botalli und Ihre Diagnose intra Vitam, Berlin, Gustav Lange, 1875

THE RÔLE OF INSULIN IN PROTEIN METABOLISM ~

N W JANNEY, M D

AND

I SHAPIRO, M D

LOS ANGELES

The question of a possible effect exerted by insulin on protein metabolism is of considerable significance both from a metabolic and a clinical standpoint. Intermediate carbohydrate metabolites are capable of synthesis together with nitrogenous compounds into protein. The well known sparing effect of carbohydrate on protein breakdown is probably due in part to such anabolic processes, as isodynamic amounts of fat fail to exert this influence. If, therefore, it could be shown experimentally that insulin increased this sparing function of carbohydrate, the conclusion would be near that this hormone probably had played a definite rôle in the synthesis of protein from carbohydrate.

To test this hypothesis, a short series of metabolic experiments were conducted in an institution especially equipped for metabolic patients, insuring accuracy in the specimen collections and in the preparation, weighing and recording of the food. The fluid intake was distributed equally during the experimental periods. Normal human subjects were placed on a fixed, weighed, mixed diet or on a practical fast for varying periods. The amount of protein sparing for a given day or period was ascertained by giving known amounts of carbohydrate. Later the effect of the addition of insulin to such glucose intake was ascertained. Urinary nitrogen and glucose were determined or tested for and in the blood, glucose, urea nitrogen and nonprotein nitrogen were determined with standard methods of analysis.

RESULTS

Insulin and glucose were found to cause additional sparing of protein over glucose alone in each of six experiments carried out on five different subjects. Therefore the series was not extended.

The total urinary nitrogen was reduced in the twelve day metabolic test from the control average of 10.83 Gm to 10.58 Gm by glucose and to 9.36 Gm by insulin and glucose (average of experiments 1 and 2). As was to be anticipated in view of the moderate amounts of glucose administered, the depressant effect on the total nitrogen was not large on the glucose days. It seemed significant, however, that the combination of insulin and glucose effected an average

~ From the Scripps Metabolic Clinic, La Jolla, San Diego, Calif

sparing of 13.6 per cent as compared to the average control nitrogen. The decrease ascribable to the superimposed effect of insulin was 11.5 per cent of the nitrogen output of the glucose days.

For the purpose of further simplification, the succeeding experiments (experiments 3, 4, 5 and 6) were conducted for shorter periods on subjects practically fasting, except for small amounts of carbohydrate given during the experimental periods. The results afford a direct comparison of the action of carbohydrate on the otherwise fasting metabolism with the same effect plus insulin administration. To avoid any possible influence of one experimental period on another, they were never consecutive.

TABLE 1—*Nitrogen Sparing Experiments (1 and 2)*

M. S., a male, weighing 64 Kg., was placed on a daily diet of 111 Gm. of carbohydrate, 70 Gm. of protein and 191 Gm. of fat. September 17, 21 and 22, 75 Gm. of glucose was given, September 18, 85 Gm., and September 18 and 22, 40 units of insulin (U 40). There were no reactions.

	Date—September, 1924											
	13	14	15	16	17*	18†	19	20	21*	22†	23	24
Total 24 hour urine nitrogen, Gm.	10.60	10.41	11.14	10.00	10.50	9.11	11.40	12.25	10.67	9.61	10.35	10.52

* Glucose given

† Glucose and insulin given

TABLE 2—*Nitrogen Sparing Experiment (3)*

H. B., a female, weighing 51 Kg., was given no food on the experiment days until 1 p. m. Glucose, 60 Gm., was given at 8 a. m., 20 Gm. at 10 a. m., 30 units of insulin (U 40) at 7:30 a. m. Date, October, 1924.

		Period				
		8 p. m. - 6 a. m. Aver. 2 Hr.	6-8 a. m.	8-10 a. m.	10 a. m. - 12 n.	12 n. - 2 p. m.
Total urine nitrogen Gm.	Glucose, day	0.60	0.51	0.85	0.81	0.42
	Glucose and insulin, day	0.54	0.47	0.71	0.67	0.33
						Total
						5.61
						4.89

In the entire series of six experiments, on the insulin-glucose day or period the nitrogen output was decreased as compared to the glucose day. In five of the six experiments the additional drop in the nitrogen, due to insulin, represented from 9.93 to 13.79 per cent of the nitrogen output obtained under the influence of glucose alone. In experiment 5, however, only a 4 per cent decrease was noted. Inquiry disclosed that this subject, who showed the lowest per kilogram nitrogen excretion of the series, was accustomed to subsist almost on a purely carbohydrate diet. This fact probably influenced the experimental result.

Nitrogen partitions at two hour intervals were carried out in experiments 3 to 6, inclusive, without definite results. They are recorded in the protocols.

TABLE 4—Blood Studies (Experiments 1-5)

[illegible]

Results of the Blood Experiments—The urea nitrogen and nonprotein nitrogen levels were followed in the blood, the protocols affording comparisons between the fasting state, the glucose and insulin-glucose periods. No consistent or very marked influence was noted in the glucose periods, the fluctuations being within the range of normal variations. After the combination of insulin and glucose, a decrease was usually found, the average fall, as compared to the fasting level, being 8.3 per cent for urea nitrogen and 5.4 per cent for nonprotein nitrogen.

Since the work of Haldane, Kay and Smith¹ has shown insulin to cause an increase in blood volume, the drop in the foregoing blood constituents after insulin may have no further significance than a dilution effect. These results cannot, therefore, be interpreted as dependable evidence for a possible removal of urea nitrogen and nonprotein nitro-

TABLE 5—*Blood Study (Experiment 6)*

Date, November, 1924 Mg. in 100 Cc		Time (Hours) After Glucose Feeding				
		Fast	$\frac{3}{4}$ Hour	2 Hours	5 Hours	8 Hours
Glucose	Glucose, day	82		74	82	88
	Insulin and glucose, day	82		30	61	85
Urea nitrogen	Glucose, day	12.9		12.3	13.2	14.6
	Insulin and glucose, day	13.9		25.0	13.6	14.6
Nonprotein nitrogen	Glucose, day	34.0		36.2	33.7	37.6
	Insulin and glucose, day	34.8		45.5	32.9	37.4

gen coincident and together with glucose from the blood to the tissues for synthetic purposes. In one instance, experiment 6, a definite increase of urea and nonprotein nitrogen was observed to accompany deep hypoglycemia, possibly a toxic manifestation.

It seemed advisable to administer substantial amounts of insulin in these experiments. In such work with normals, it was found practically impossible to avoid insulin reactions. In spite of rather profound hypoglycemia noted in several instances, the reactions went no further than perspiration and weakness. The subjects remained perfectly quiet. Therefore, it seems unlikely that toxic phenomena or increased muscular activity has perceptibly influenced the nitrogen urinary excretion, particularly when one recollects that a toxic effect on protein metabolism usually results in a loss of cell substance, hence an increase rather than the observed decrease in the nitrogen output.

1 Haldane, J. B. S., Kay, H. D., and Smith, W. *J. Physiol.* **59** 193 (Oct) 1924.

COMMENT

There are but three possibilities concerning the action of insulin according to Macleod's² logical analysis, as follows. Insulin can cause hypoglycemia, either by (1) direct action on the blood, (2) blocking of glycogenolysis in the liver or muscles, and (3) acceleration of glucose consumption in tissues.

1 Direct action on the blood can be excluded by the negative results of glycolysis experiments.³ Yet according to Winter and Smith⁴ it is still possible that insulin might affect stereochemical changes in the blood glucose molecule, rendering it more labile. The pertinent experimental evidence and conclusions supporting this interesting hypothesis have, however, failed of substantiation.⁵

2 Blocking of glycogenolysis in the liver would cause hypoglycemia if consumption of glucose in tissue were normal. This view is unacceptable as, after insulin injections, glucose disappears from blood of hepatised animals at the same rate as in normal animals. When insulin is given to sound animals, glucose disappears indeed much more rapidly than in the case of hepatised animals without insulin.

3 By exclusion, therefore, the action of insulin must be on the tissues, and insulin hypoglycemia must ensue as a result of the demand for glucose set up by insulin in the tissues.

It becomes of great importance to determine whether the liver is the chief seat of insulin action, on account of the rôle played by this organ in carbohydrate metabolism. Recent important perfusion experiments by Burn and Dale⁶ with hepatised and eviscerated animals demonstrate that the liver cannot be of prime importance in insulin metabolism, as the heart and skeletal muscles are largely responsible for disappearance of glucose under insulin influence. Previously the liver was shown to be unessential to the action of insulin by Mann and Magath,⁷ as was also the case with the brain as demonstrated by Olmsted and Logan.⁸ Hepburn and Latchford⁹ and also Thalhimer have noted the same in studying heart preparation, also Cori, Cori and Goltz¹⁰ and Lawrence¹¹ in study of perfused limbs. This evidence does not dis-

2 Macleod, J. J. R. *Physiol Rev* 4 21 (Jan) 1924

3 Eadie, G. S. Macleod, J. J. R., and Noble, E. C. *Am J Physiol* 65 462 (Aug) 1923

4 Winter, L. B., and Smith, W. *Brit M J* 1 711 (April 28) 1923

5 Eadie, G. S., Macleod, J. J. R., and Noble, E. C. *Am J Physiol* 72 614 (May) 1925

6 Burn, J. H. and Dale, H. H. *J Physiol* 59 165 (Oct) 1924

7 Mann, F. C. and Magath, T. B. *Am J Physiol* 65 403 (July) 1923

8 Olmsted, J. M. D., and Logan, H. D. *Am J Physiol* 66 437 (Oct) 1923

9 Hepburn, J. and Latchford, I. K. *Am J Physiol* 62 177 (Sept) 1922

10 Cori, G. T., Cori, C. F., and Goltz, H. L. *J Pharm & Exper Therap* 22 355 (Dec) 1923

11 Lawrence, R. D. *Brit M J* 1 516 (March 22) 1924

prove, however, that the liver is equally concerned with all the organs in the function of insulin, which indeed is likely

As the action of insulin cannot depend on a special function of the liver, it is even possible that the effect of insulin on glycogen may be secondary and only incidental to its general function in the tissues involving a demand for glucose. Certainly insulin does not promote glycogen formation in the liver of normal animals,¹² and causes glycogen already deposited in normal muscles and liver to decrease in amount.¹³ The loss of glycogen is evidently due to the glucose hunger of the tissues.

The Fate of Glucose Metabolized by Insulin—The following facts have been ascertained from recent animal respiratory work with insulin. When muscular activity and other disturbing factors are properly controlled, the oxygen intake is usually transiently and slightly increased or even decreased as a result of insulin action. The respiratory quotient may become a little elevated or remain about unity. These results taken as a whole indicate that oxidative processes are initiated by insulin, but the amount of oxygen thus absorbed is insufficient to account for disappearance of much of the sugar through combustion. Conversion into fat can be excluded in all but a few instances. The metabolism is changed quantitatively in that more carbohydrate enters into the process. Disappearance of such glucose is best accounted for by its conversion into some unknown substance, neither fat nor carbohydrate.¹⁴ The relation of lactic acid to glycolysis by insulin has not been definitely determined. The diminution of blood phosphates as a result of insulin action is likewise accounted for by an *oxidative synthetic process* according to Winter and Smith¹⁵ and by Brugsch.¹⁶

THE RELATION OF INSULIN TO PROTEIN METABOLISM

Experimental data are scanty as attention has been hitherto focused on the relation of insulin to diabetes, hence to carbohydrate metabolism. Decreased nitrogen output in a dog on high protein diet and insulin has

12 McCormick, N. A., Macleod, J. J. R., and O'Brien, M. K. *Tr. Roy. Soc. Canada* **17** 57, 1923. Dudley and Marrian. *Biochem. J.* **17** 435, 1923.

13 Dudley and Marrian (Footnote 12, second reference). Brugsch, I. T., Benatt, A., Hoisters, H., and Katz, R. *Biochem. Ztschr.* **147** 112, 1924.

14 Krogh, A. *Deutsche med. Wchnschr.* **49** 1321 (Oct. 19) 1923. Eadie, G. S., and Macleod, J. J. R. *Am. J. Physiol.* **64** 285 (April) 1923. Burn and Dale (Footnote 6). Brugsch, T. *Deutsche med. Wchnschr.* **50** 491 (April 18) 1924.

15 Winter, L. B., and Smith, W. *J. Physiol.* **58** 327 (March) 1924.

16 Brugsch (Footnote 14, fourth reference).

been reported by Macleod and Frank N Allan¹⁷ Protein sparing as a result of insulin administration in diabetic cases has been noted by Fitz, Murphy and Grant¹⁸ In their insulin dosage studies, certain of Olmsted and Kahn's¹⁹ protocols, for example case 6, show definite protein sparing in diabetes as a result of insulin administration The experimental evidence submitted in the present article demonstrates that, in normal human subjects, the protein sparing action of carbohydrate is increased by insulin

CARBOHYDRATES AND PROTEIN SYNTHESIS

Before discussing the possible relation of insulin to protein it seems expedient to emphasize that carbohydrate metabolites probably *normally* enter into protein synthesis The immense pertinent data can be but alluded to here A critical analysis of the same up to 1918 was made by one of us²⁰ Much confirmatory evidence has been added thereafter, for example, the synthetic possibilities of the ketonic aldehydes derived from carbohydrates are now known (Dakin and Dudley)

The theory that carbohydrate or its metabolites enters into the synthesis of protein was supported by Kassowitz, Paton and Cathcart among many others on the basis of the protein sparing action of carbohydrate, as has been demonstrated by Landergren,²¹ Cederereutz,²² Cathcart,²³ Kayser²⁴ and Ringer²⁵ It has thus been fairly established that, under both experimental and normal conditions in animals and man, (1) carbohydrate is necessary for the retention of nitrogen, (2) carbohydrate is so urgently required that, should it be deficient in the diet, tissue protein is catabolized to supply carbohydrate metabolites even when the dietary contains an adequate amount of protein and fat for ordinary metabolic and fuel requirements, (3) a purely dynamic hypothesis, such as simple fuel replacement, fails to account for this specific function of carbohydrate

17 Macleod, J J R, and Allan, F N Tr Roy Soc Canada **17** 47, 1923

18 Fitz, R, Murphy, W P, and Grant, S B J Metab Research **2** 753 (Nov-Dec) 1922

19 Olmsted, W H, and Kahn, S H Boston M & S J **190** 1018 (June 12) 1924

20 Janney, N W New York M J, May 4 and 11, 1918

21 Landergren, E Skandin Arch f Physiol **14** 112, 1903

22 Cederereutz, A Beitrage zur Kenntniss des Stoffwechsels in der Fruhperiode der Syphilis nebst Untersuchungen uber die Einwirkung therapeutischer Quecksilver und Jod-Kali Gaben an der Stoffwechsel des Menschen, Breslau, 1902

23 Cathcart, E P J Physiol **34** 311, 1909-1910, The Physiology of Protein Metabolism, London, 1912

24 Kayser Du Bois Arch, 1893, p 371

25 Ringer, A I J Biol Chem **12** 431, 1912

Ingested amino-acids are immediately deaminized very completely as shown by Levene and others. The older view that the amino-acids of the food are directly incorporated as such into new protein is no longer tenable. With few exceptions it may be regarded as practically demonstrated that tissue amino-acids, hence protein, may be freely synthesized from the split products of ingested amino-acids, carbohydrate metabolites and various nitrogenous compounds. As a classic example, alanine has long been known to be formed in perfused liver from glycogen and ammonium chloride²⁶. Much evidence has now accumulated supporting the modern point of view that ingested and body protein, carbohydrates and fats undergo catabolism into various intermediary metabolites which are continuously built by a *process of selective synthesis* into higher products, including protein, which is required by the wear and tear of living tissues. This is the only possible explanation of the remarkable and elaborate experiments of Osborne, Mendel and co-workers, who demonstrated the maintenance and even propagation of carnivora (mice) on a diet, the nitrogen of which was supplied by a single amino-acid.

INSULIN AND PROTEIN SYNTHESIS

If we accept, then, that carbohydrate metabolites probably enter into protein synthesis, what rôle, if any, does insulin play in this process? Present evidence, it must be admitted, is mostly indirect and presumptive.

To recapitulate, protoplasmic organs, particularly the muscles, show a remarkable affinity for carbohydrate, especially for glucose. The need for carbohydrate is so vital that a glycogen reserve is maintained by a special metabolism against such need. All the protoplasmic organs, and no special one, are the seat of activity of insulin. Therefore, insulin action is a general one on protoplasm. Permeability of cells is markedly increased by insulin¹. The breakdown of protein, in animals²⁷ and in normal men and women (demonstrated by experiments in this article), can be inhibited by insulin. Large amounts of glucose disappear in the tissues under the influence of insulin, and in careful respiratory quotient experiments, such glucose cannot be accounted for by combustion alone²⁷. As direct evidence that insulin actively aids protein synthesis it seems that we have only the important observation of Gey and Thalhimer,²⁸ who, using Carrel's tissue growing methods, obtained a much greater growth of such cultures on addition of insulin and glu-

26 Knoop, F. *Ztschr. f. physiol. Chem.* **67** 489, 1910. Embden, G., and Schmitz, E. *Biochem. Ztschr.* **29** 423, 1910.

27 Macleod (Footnote 2), Burn and Dale (Footnote 6).

28 Gey, G. O., and Thalhimer, W. *J. A. M. A.* **82** 1609 (May 17) 1924.

cose than could be obtained by glucose alone. Further experimentation of this kind is urgently indicated.

However deficient the foregoing evidence as a whole may be regarded, yet it has a decided value from the standpoint of exclusion. Thus it is impossible to account for the disappearance of glucose in animal tissues without acceptance of the theory that it is transformed into material no longer having the chemical characteristics of glucose and involving oxidative processes²⁹. Neither fat nor glycogen nor carbohydrate metabolites, such as lactic acid, are found to accumulate in sufficient quantity in such periods of active metabolism to account for the mass of such disappearing glucose. Recollecting, then, the constant need of replacement, repair and regeneration of old protein, as well as growth of new, and the fact that such glucose utilization is now demonstrated to be a function of insulin, *it seems possible that carbohydrate metabolites are synthesized into the protein molecule by the aid of insulin*. This conception leaves the question open as to whether such actual syntheses are ultimately a function of the tissue enzymes or of insulin. Insulin's rôle may be limited to the preparation of certain labile intermediary carbohydrate metabolites indispensable for protein synthesis.

INSULIN AND PROTEIN METABOLISM IN DIABETES

According to evidence presented and discussed in this article, the sparing action of insulin on protein metabolism takes place in both the normal and the diabetic subject, which would indicate that so far as the effect of insulin is concerned, there is no appreciable difference in either case. The chief point of divergence seems to lie in the deficient supply of insulin in diabetes, and the disastrous effect of this lack on protein and possibly also on fat metabolism. The increase in protein breakdown in severe diabetes was formerly regarded as due to fuel purposes alone, i. e., to replace carbohydrate incapable of combustion, or in the second place as due to acidosis poisoning. It seems, however, that this process is really more complicated. It is well to recollect that body protein, constituting vital tissue, is never broken down for fuel if sufficient carbohydrate or fat is present. Yet in the preinsulin treatment of diabetes, the isodynamic replacement of carbohydrate, fuel that could not be burned with fat failed to prevent protein breakdown in the severest diabetes, precisely as in Landergren's classical protein sparing experiments on normals. As Woodyatt has clearly shown part of this protein destruction may take place in order to supply carbohydrate should this be deficient in the diet. The diabetic metabolism here reacts just the same as the normal, for in either a

29 Macleod (Footnote 2) Burn and Dale (Footnote 6) Brugsch (Footnote 14, fourth reference)

certain amount of carbohydrate or carbohydrate metabolites seems indispensable. If not contained in the food, protein must be broken down to supply the deficiency. The acidosis and protein breakdown of diabetes may be regarded as strictly analogous to that of inanition. In both conditions there is a shortage of constituents of protein *Bausteme*, in the case of diabetes through failure of the insulin supply, in inanition, through failure of the food supply. Increased protein catabolism would be due in either case partly for fuel purposes and partly to supply the intermediary products for synthetic repair processes in other protoplasm of prime importance, such as the heart and the brain. It is well to keep in mind the conception of "protein starvation in diabetes," a type of starvation so severe that no ingenious balancing during preinsulin therapy of rations could withstay its lethal termination in severe cases.

The relation of acidosis to this "anabolic conception" of diabetic metabolism requires mention. Without attempting to launch far into the tempestuous sea of intermediary metabolism, the following seems clear. In diabetes, the catabolism of protein and fat is accompanied by the excretion of B-oxybutyric acid and diacetic acid, among other products. Giving of glucose may partially remove such acid products, but insulin and glucose given together promptly clear up such so-called acidosis. It seems, then, logical to conclude that insulin aids either in the oxidation of these intermediary products or in their removal, or in that of their precursors, by transformation into other material, probably by synthesis with intermediary carbohydrate products. Acidosis in diabetes had best be defined as demonstrable signs of protein starvation, or the blocking of fat metabolism, rather than a clinical state, the so-called acidosis poisoning. The weak point in the acidosis poisoning theory has always been the fact that while most patients in diabetic coma enter this condition with profound acidosis, yet there are others who after slight trauma, infections and the like become comatose with but few demonstrable signs of acidosis. Both of these types may show a prelethal rise of nitrogen metabolism.

It is notable that, if given in time, insulin saves cases in both these categories. If we keep in mind the intimate relation of carbohydrate and protein metabolism, it seems possible that the symptoms of diabetic coma may develop just as in other terminal comas induced by such conditions as starvation, poisoning and sepsis, as a result and expression of extensive cellular death. Death of the affected organism will ensue if repair and regenerative processes fail to recuperate the loss promptly. Thus it seems more reasonable to account for diabetic coma as an end-result of protein starvation, rather than to overforce the acidosis etiology in the face of diametrically opposed laboratory and clinical data. Certainly the failure of carbohydrate administration alone, or of

insulin with insufficient carbohydrate, suggests an intimate relation between insulin, carbohydrate and cellular metabolism. It seems particularly significant that cessation of protein breakdown ushers in the clinical recovery of such coma cases.

Certain other clinical observations would tend to support such a point of view. For example, diabetes is particularly severe in children. Under preinsulin treatment, they tended to grow slowly even when supplied with sufficient food calorically. Normal growth, which is but the outward and visible sign of active protein synthesis, is rapidly restored with insulin, as is well known. In diabetic adults, resistance to infection and fatigue is frequently observed to result from the administration of a few units of insulin, even when no caloric increase of diet had been instituted.

USE OF INSULIN IN NONDIABETIC CONDITIONS

It is believed that the data reported in this article afford a logical basis for the thorough trial of the insulin-carbohydrate treatment in nondiabetic conditions involving strain on the protein tissues. Such conditions would be prolonged infections, sepsis, malnutrition, nondiabetic toxic and comatose states, also trauma, particularly when accompanied by acidosis. Some encouraging steps have already been taken in this direction, particularly in the treatment of operative trauma and the toxemia of pregnancy³⁰.

SUMMARY AND CONCLUSIONS

1 *The seat of activity of insulin is in the protein tissues.* Data from the literature establish that the seat of insulin activity lies in the tissue cells of the entire organism. Large amounts of glucose disappear in the tissues during insulin activity. Such utilization of carbohydrate can be accounted for only by conversion into material other than glucose, and not by total combustion alone.

2 *Protein sparing by carbohydrate is increased by insulin.* Experimental evidence is recorded demonstrating, in normal human subjects, that insulin and carbohydrate spare more protein than does carbohydrate alone. As protein sparing by carbohydrate is probably an expression of protein synthesis from carbohydrate metabolites, the data here reported would indicate that insulin functions in aiding protein synthesis from carbohydrate, probably by providing necessary metabolites. Hence, insulin has an anabolic (protogenic) as well as a catabolic (glycolytic) function.

³⁰ Thalhimer, W. Surg Gynec Obst **39** 237 (Aug.) 1924. Fisher, D., and Snell, N. W. J. A. M. A. **82** 699 (March 1) 1924.

3 *Diabetes may be a result of deficient protein anabolism* The foregoing data indicate that the ultimate disturbance in diabetic metabolism may be deficiency in the replacement, regeneration and repair of protoplasm due to the lack of carbohydrate metabolites normally provided by the insulin. This hypothesis affords a rather attractive explanation for diabetic metabolism and symptomatology as follows:

Diabetic metabolism is characterized by protein loss, acidosis, adiposity and lipemia, in addition to glycosuria and hyperglycemia.

In the severest diabetes, untreated with insulin, the body protein loss continues in spite of replacement, in the diet, by food protein and fat of the inutilizable carbohydrate. Protein loss must therefore be due to other than dynamic reasons alone. Such a specific breakdown of protein can be adequately explained as resulting from a lack of normal protein regeneration from indispensable carbohydrate metabolites supplied, in health, by insulin.

Such protoplasmic starvation, if prolonged, could lead to extensive cellular exhaustion and ultimately to death of the organism. Diabetic coma may be the clinical expression of such changes. Strain on the protein tissues would hasten the onset of such coma, which may be accompanied by a prelethal rise in the nitrogen output. Acute infections, trauma and pregnancy, common causes of diabetic coma, exert strain on the protein tissues.

The acidosis theory of diabetic coma is untenable, as coma may intervene with but mild acidosis. An increase of acid bodies results from protein loss and abnormal fat metabolism, which again may possibly be due to lack of certain specific carbohydrate cleavage products normally supplied through the functioning of insulin. "Acidosis" is to be regarded as an effect rather than a cause of this process. Diabetic adiposity and lipemia may possibly arise from fatty carbon chains by aldol condensation of carbohydrate metabolites normally entering into protein synthesis.

Impairment of protoplasmic repair processes can likewise account for the proneness to infection and slow healing exhibited by diabetic tissues, retardation of growth in young diabetic patients, and muscular weakness in diabetic patients even on balanced diets.

The return to normal of the diabetic patient treated by insulin would indicate that all the various metabolic and clinical manifestations of diabetes are due to one general cause, presumably the failure of utilization of carbohydrate. This "anabolic conception of diabetes" likewise recognizes one general cause, failure of utilization of supply of carbohydrate metabolites necessary for protein regeneration. The loss of carbohydrate fuel fails to account adequately for the total metabolic and clinical manifestations of diabetes.

4 *Metabolism of manition* The metabolism of manition may be explained on an analogous basis. The lack of carbohydrate metabolites, as well as protein, in the food produces results similar to the lack of insulin in diabetes, namely, protein loss in addition to dynamic causes, acidosis and prelethal rise in nitrogen excretion. Administration of carbohydrate but not fat reduces the protein loss to a minimum, as insulin is present in abundance.

5 *Insulin-carbohydrate therapy in nondiabetic conditions* Experimental support is herewith afforded for the extension of insulin therapy to various nondiabetic conditions, characterized by protoplasmic strain on tissues, such as manition, trauma and sepsis.

THE RELATIVE IMPORTANCE OF THE SYSTOLIC AND THE DIASTOLIC BLOOD PRESSURE IN MAINTAINING THE CORONARY CIRCULATION

FRED M SMITH, M D

G H MILLER, M D

AND

V C GRABER, M D

IOWA CITY

It is generally known that the coronary circulation is greatly influenced by changes in blood pressure. This was well illustrated by the experiments of Markwalder and Starling¹. In some instances they obtained 100 per cent increase in the rate of coronary flow by elevating the blood pressure from 80 to 110 mm of mercury. The relative importance of the two phases of the blood pressure in maintaining the coronary circulation, however, has not been determined. In the study of the coronary circulation in the tortoise, the blood was observed to flow very rapidly during the diastolic phase, whereas during the height of the systolic period the smaller arteries were closed and the blood came to a standstill in the larger vessels². It would thus seem that the rate of coronary flow is to a large extent dependent on the height of the diastolic pressure. It is therefore not improbable that the disturbance in the coronary circulation resulting from the decreased diastolic pressure in aortic regurgitation and arteriovenous aneurysm may be partially responsible for the increase in the size of the heart, and later the onset of cardiac failure. The observations of Cazamian³ and Leriche,⁴ in which a decrease in the size of the heart was noted following the repair of arteriovenous aneurysm favors this conception. In the case reported by the latter there were, in addition to the increase in the size of the heart, clinical manifestations of cardiac failure. Following the operation the signs of cardiac failure disappeared and the heart returned to the normal size.

Lewis⁵ has shown that the arterial phenomena in arteriovenous aneurysm and aortic regurgitation which are fundamentally dependent on the decrease in the diastolic pressure with an increase in the pulse

* From the State University of Iowa College of Medicine

* Read before the American Society for Clinical Investigation, Atlantic City, N J, May 3, 1926

1 Markwalder, Josif and Starling E H J Physiol **47** 275, 1913-1914

2 Drury, A N, and Smith, F M Heart **11** 71 (Jan) 1924

3 Cazamian Bull et mem Soc med d hop de Paris **41** 46, 1917

4 Leriche Lyon chir **16** 427 1919

5 Lewis, T, and Drury A N Heart **10** 301, 1923

pressure, are similar. He suggested that the cardiac enlargement in these conditions was due to a deficient nutrition of the heart muscle resulting from the decrease in the mean arterial pressure. This conclusion was based on the study of the circulation of the limbs and he assumed that comparable changes occurred in the flow through the coronary arteries.

The object of this investigation was to determine the effects of specific changes in the systolic and the diastolic pressure on the coronary circulation.

METHOD

Dogs were employed in this series of experiments. These animals were prepared by a preliminary injection of morphine and a subsequent administration of chlorbutanol by stomach tube. Ether was used in sufficient amounts to complete the anesthesia. The blood pressure was recorded on the kymograph by a Straub membrane monometer. This instrument was employed in order to obtain a more accurate record of the systolic and the diastolic pressure. The chest was opened in the median line and a Morawitz-Zahn cannula⁶ was introduced into the coronary sinus through the right auricular tip. The blood was prevented from coagulating by the use of heparin. The flow from the coronary sinus was allowed to escape into a 50 cc graduate. These amounts were registered on the kymograph. The blood was maintained at body temperature and reintroduced into the femoral vein. Changes in the blood pressure were produced by constricting the thoracic aorta with an adjustable clamp and by the experimental production of arteriovenous aneurysm and aortic regurgitation. The arteriovenous aneurysm was produced by conducting the flow of the blood from a carotid artery through a small rubber bag to the jugular vein of the opposite side. The rubber bag was employed in order that the jugular vein might not be subjected to the full arterial pressure. The aortic regurgitation was produced by puncturing the aortic valves by means of a small wire introduced into the aorta through the carotid artery.

In those experiments in which the thoracic aorta was constricted by an adjustable clamp, it was possible, within certain limits, to increase the diastolic pressure without altering the systolic pressure. A typical experiment of this type is illustrated in figure 1. During the control period of this experiment the systolic pressure was 150 mm of mercury and the diastolic 50. The rate of flow from the coronary sinus was 120 cc per minute. After the aorta was constricted the diastolic pressure arose to 83 mm of mercury and the systolic decreased to 145 and the flow from the coronary sinus increased to 187 cc per minute. There was thus associated with the elevation of the diastolic pressure a striking

6 Morawitz and Zahn. *Zentralbl f Physiol* 26:465, 1912.

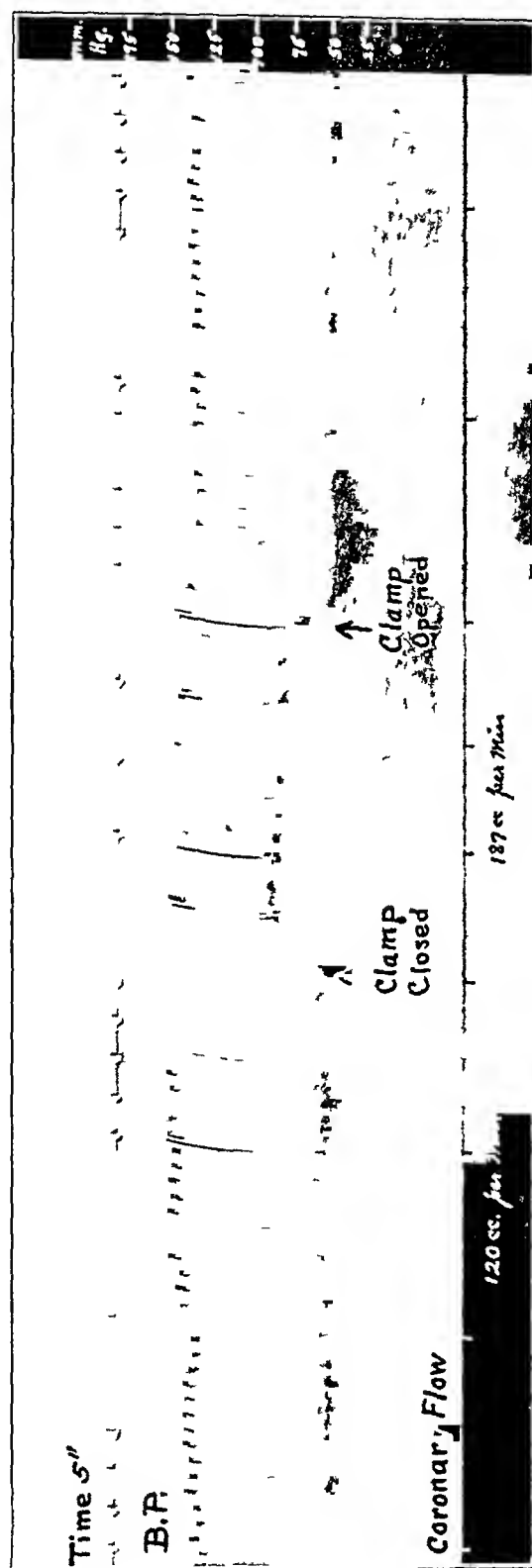


Fig 1—Effect of constricting the thoracic aorta with an adjustable clamp diastolic pressure increased 66 per cent, coronary flow increased 56 per cent

increase in the rate of coronary flow even though the systolic pressure was slightly reduced. In all the experiments of this type the rate of coronary flow was increased and the percentage of increase was roughly proportional to the elevation of the diastolic pressure.

When the arteriovenous aneurysm was employed the diastolic pressure was reduced and the systolic increased. The alterations in the blood pressure and the associated changes in the coronary flow produced by this method are demonstrated by the experiment shown in figure 2. In this experiment, following the opening of the aneurysm, the systolic pressure increased from 155 to 165 mm of mercury and the diastolic pressure fell from 72 to 57. The flow from the coronary sinus decreased from 180 to 157 cc per minute. There was thus a 21 per cent reduction in the diastolic pressure and a 13 per cent decrease in the rate of coronary flow even though there was an increase in the systolic pressure of 10 mm. In all the experiments of this group similar results were obtained.

In the experiments in which an aortic regurgitation was produced by puncturing the aortic valves, the results were similar to those of the arteriovenous aneurysm. The systolic pressure was increased, the diastolic decreased and there were corresponding changes in the coronary flow. The alterations in the blood pressure and the changes in the coronary flow varied with the extent to which the aortic valves were damaged. The results of one of these experiments is shown in figure 3. In the control period (fig 3 *a*) the systolic pressure was 110 and the diastolic 50. The rate of flow from the coronary sinus was 240 cc per minute. Following the puncture of one valve (fig 3 *b*) the systolic pressure was increased to 120 and the diastolic fell to 30. The flow from the coronary sinus was reduced to 195 cc per minute. Later the same valve cusp was torn loose from its base. Following this procedure (fig 3 *c*) the systolic pressure at once increased to 150 and the diastolic fell to 15. The flow from the coronary sinus was further reduced to 150 cc per minute. Even though the systolic pressure was increased 50 mm of mercury over that of the control period, the rate of flow from the coronary sinus was decreased 90 cc per minute. In other experiments of this nature comparable results were obtained.

CONCLUSIONS

The results of this series of experiments show that the rate of coronary flow is greatly altered by changes in the diastolic pressure, even in the presence of changes in the systolic pressure in the opposite direction. In one instance in which there was a reduction of only 5 mm of mercury in the diastolic pressure associated with an increase of 10 in the systolic pressure, there was a decrease in the flow of the blood from the coronary sinus from 277 to 250 cc per minute. Similarly in

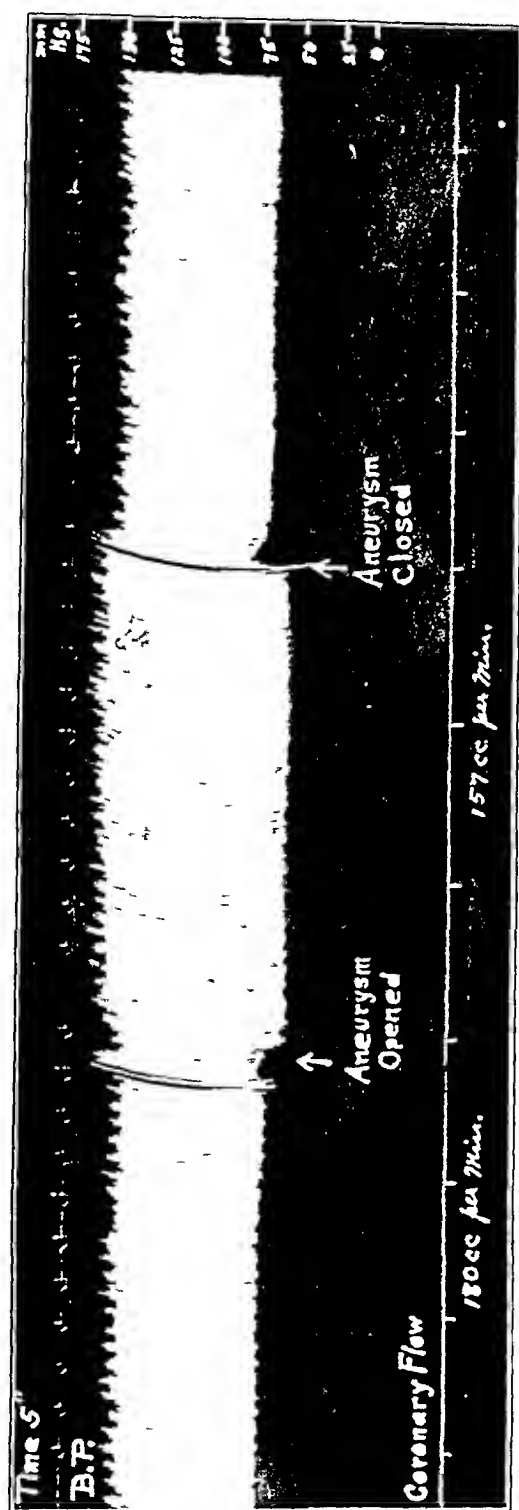


Fig 2—Effect of artificial arteriovenous aneurysm on coronary flow diastolic pressure decreased 21 per cent, coronary flow decreased 13 per cent

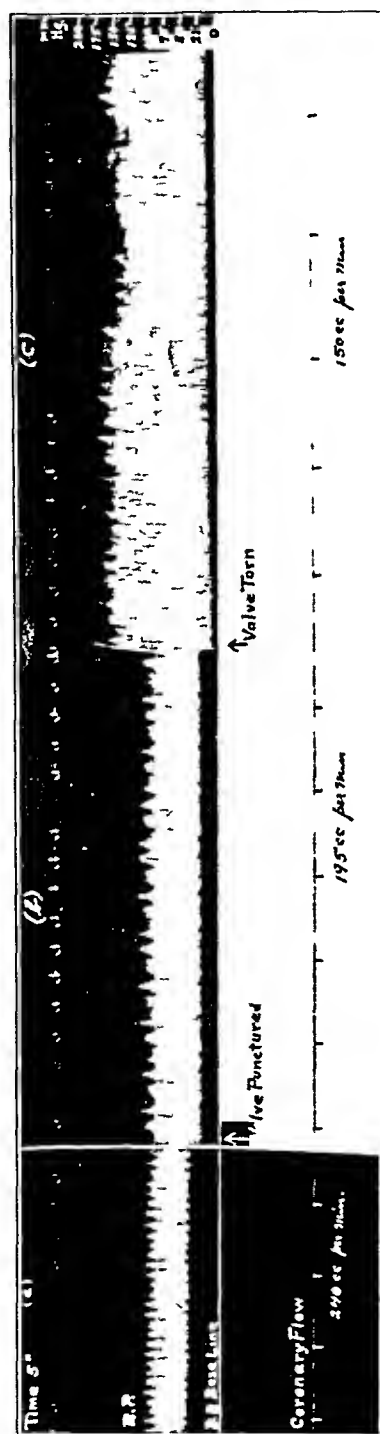


Fig 3—Effect of aortic regurgitation on coronary flow *a*, control period, *b*, one valve cusp punctured diastolic pressure decreased 40 per cent, coronary flow decreased 20 per cent, *c*, one valve torn loose diastolic pressure decreased 70 per cent, coronary flow decreased 37 per cent

those experiments in which there was a corresponding elevation of the diastolic pressure, even though the systolic pressure remained constant or was even slightly reduced there was a comparable increase in the rate of coronary flow. It is evident from these results that the maintenance of an efficient coronary circulation is fundamentally dependent on the height of the diastolic pressure. It is not to be inferred, however, that the changes in the systolic pressure are entirely without influence on the rate of coronary flow. In experiments in which the diastolic pressure was reduced to a permanent low level, as in figure 3 *c* the rate of coronary flow may further be reduced by decreasing the systolic pressure and again increased by elevating the systolic blood pressure. In figure 3 *c*, however, even though the systolic pressure is 150, the flow from the coronary sinus is 90 cc per minute less than during the control period (fig 3 *a*). While the systolic phase of the blood pressure may, to a certain extent, influence the coronary flow, it is certainly subordinate to that of the diastolic pressure in maintaining the coronary circulation.

On the basis of these findings it would seem that the decreased coronary flow associated with the diminished diastolic pressure in aortic regurgitation and arteriovenous aneurysm is probably a significant factor in the development of the cardiac hypertrophy and, later, cardiac failure.

AURICULAR FIBRILLATION WITH REGULAR VENTRICULAR RHYTHM AND RATE OVER SIXTY *

ROBERT L. LEVY, M.D.
NEW YORK

The outstanding clinical feature of the cardiac arrhythmia now known to be associated with fibrillation of the auricles is irregularity of the ventricular beat. Before use of the electrocardiographic method made possible the recognition of the underlying disturbance in mechanism, the condition was termed *pulsus irregularis perpetuus*. The irregularity is not, however, invariably permanent. It may occur as paroxysms which terminate spontaneously, or a drug, such as quinidine, may be employed to restore sinus rhythm. It is also known that there may be complete heart block in auricular fibrillation, often the result of the therapeutic use of digitalis. As an accompaniment of A-V dissociation, regular idioventricular rhythm is established, usually at rates ranging from 30 to 40, though occasionally higher when the impulse is initiated in the junctional tissues.

More rarely it may be noted that, for varying periods, the ventricles, though beating at a rate of 60 or over, contract regularly. Such an event is of diagnostic importance in that it immediately presents the possibility that normal rhythm has spontaneously been resumed. Such was the opinion expressed in two of the cases shortly to be presented, until an electrocardiogram indicated that the auricles were still fibrillating. The occurrence of regular, rapid ventricular rhythm is worthy, as well, of theoretical consideration in relation to the analogy between fibrillation and flutter and their dependence on circus movement in the auricles.

During a three year period four cases were observed in which auricular fibrillation was associated with regular ventricular rhythm and rate over 60. In one of these patients (case 2) this change in rhythm occurred five times at intervals of a month or more, in another (case 4), in whom regularity was always interrupted by occasional interventricular intervals of unequal length, it was recorded three times in as many weeks. During the same three years, 227 patients with auricular fibrillation had records made in the cardiographic laboratory. According to these figures, the occurrence of regular ventricular rhythm with rate over 60 is uncommon in auricular fibrillation having been recorded in less than 2 per cent of the cases.

* From the Department of Medicine of the Columbia University College of Physicians and Surgeons, and the Presbyterian Hospital.

REPORT OF CASES

CASE 1—J S, a girl aged 16 years, was admitted for the second time, Feb 11 1925, and died March 26. The diagnosis was cardiac hypertrophy, chronic cardiac valvular disease, mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation, cardiac insufficiency, and erysipelas.

There was history of diphtheria and scarlet fever in childhood and frequent attacks of tonsillitis. At 9, she had rheumatic fever, with a mild recrudescence at 12 for which she was admitted to the hospital in 1921, remaining six weeks.

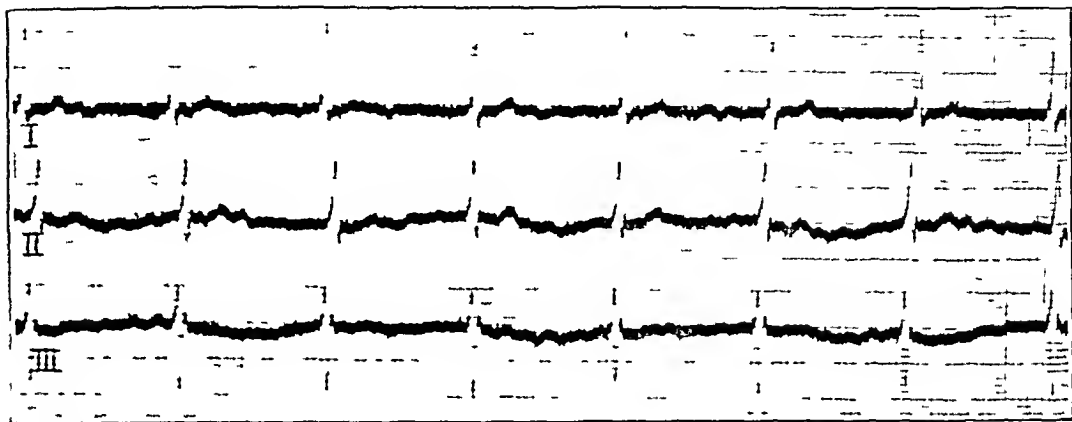


Fig 1 (case 1) —Leads I, II and III, showing regular ventricular rhythm with rate of 74.

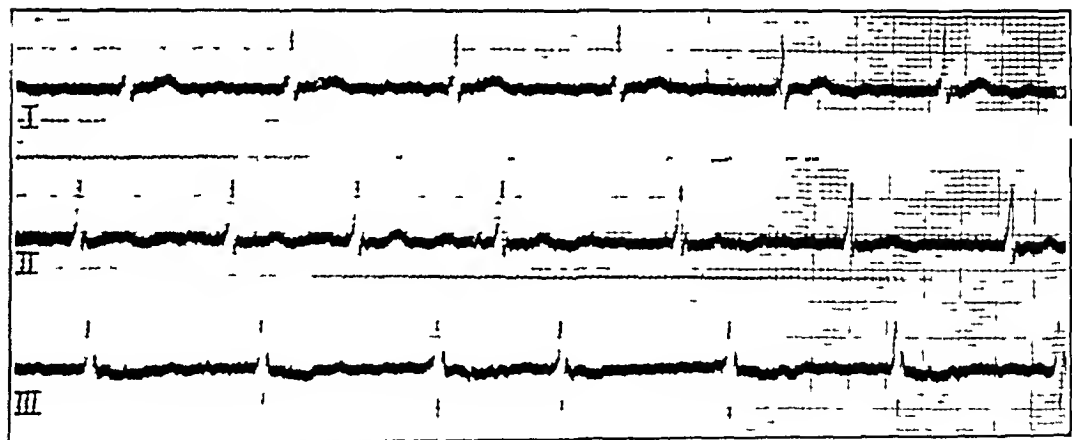


Fig 2 (case 1) —Leads I, II and III, two days later than figure 1, showing regular ventricular rhythm with rate of 70 in Lead I, irregular rhythm in Leads II and III. It should be noted that there is no significant difference in the form of the complexes in the two sets of records.

Auricular fibrillation was first observed in November, 1923. There were progressive symptoms of cardiac failure, aggravated by frequent respiratory infections. Three days before death, erysipelas of the face appeared and hastened the end. Necropsy was not performed.

At the time of the final admission, February 11, there were signs of diffuse bilateral bronchitis, with probable patches of bronchopneumonia. The temperature was 102.8 but fell to a normal level in three days. Subsequently, there were irregular elevations to 102, interrupted by afebrile periods of several days. The heart was greatly enlarged. The rhythm was irregular, the apex rate 72, with small pulse deficit. The liver was swollen and there was moderate peripheral

edema The white blood cells totaled 17,200, with 79 per cent polymorphonuclears, the red blood cells, 3,420,000, and hemoglobin, 60 per cent

Prior to admission she had been taking two tablets of about 0.12 Gm of digitalis daily for a number of weeks During the first eight days in the hospital, she received 9 cc of the tincture of digitalis, 2 cc being given on the first day and 1 cc daily thereafter, the drug having been omitted on the fourth day At her own request, the digitalis in tablet form was then resumed, two tablets being given daily for ten days During these nineteen days, the heart rate ranged from

TABLE 1—Case 1—J S, Aged 15

Date 1925	Electro- cardio- gram	Digitalis (Tincture)	Ventric- ular Rhythm	Ventric- ular Rate	T Wave			Remarks
					I	II	III	
March 9	7501	None for 6 days until March 8, when 2 cc was given	Regular	74	+	+	—	Temperature, 101.4, bedside notes de- scribe regularity of rhythm
March 10	7511	1 cc March 9	Regular	72	+	+	—	Temperature, 101.2
March 11	7516	1 cc March 10	Regular + Irregular	70	+	+	—	Temperature, 100.6
March 12	7525	None	Irregular	72	+	+	—	Temperature, 100

TABLE 2—Case 1—Interventricular Intervals (Seconds)

	Figure 1 Rate 74	Electrocardiogram 7511 Rate 72	Figure 2 Rate 70
	0.82	0.82	0.86
	0.81	0.73	0.77*
	0.81	0.81	0.88
	0.81	0.77	0.87
	0.82	0.83	0.88
	0.82	0.82	0.88
	0.81	0.80	0.88
	0.74	0.80	0.88
	0.78	0.80	0.81
	0.79	0.83	0.90
	0.75	0.83	0.90
	0.80	0.83	0.92
	0.80	0.83	0.90
	0.81	0.84	0.81
	0.81	0.82	0.66*
	0.79	0.82	0.77*
	0.80	0.84	0.96
	0.81	0.83	0.92
	0.79	0.82	0.88
	0.79	0.83	0.92
	0.81	0.85	0.65*
	0.81	0.83	0.90
	0.80	0.84	0.79*
		0.83	0.91
		0.83	0.92
			0.95
			0.66*
			0.90
			0.89
			0.88
			0.69*
			0.87
Maximum variation (seconds) exclusive of those marked with in asterisk (*)	0.08	0.11	0.12

60 to 80, with little or no pulse deficit No digitalis was given from March 2 to 7, inclusive March 8, 2 cc of tincture were given because of slight fever and elevation of heart rate to 100 The electrocardiogram, March 9, showed auricular fibrillation with regular ventricular rhythm and rate of 74 (table 1 and fig 1) There was moderate left ventricular preponderance The general form of the ventricular complexes resembled that of curves made several days previously when the rhythm was totally irregular and the rate 65 March 10 and 11, 1 cc of tincture of digitalis was given March 10, the rhythm was still perfectly regular,

March 11, portions of the record showed sequences of normal beats, while in places irregularity was noted (table 2). The rate was 80. March 12, the rhythm was again completely irregular, the rate being 72. The arrhythmia persisted with varying rates, until death fourteen days later. There were no form changes in the later graphic records.

CASE 2—J. W., a boy aged 13 years, admitted for the third time, July 3, 1922, and discharged improved, July 22, 1923, died in his sleep, Aug. 12, 1924. The diagnosis was chronic rheumatic fever, cardiac hypertrophy, chronic cardiac valvular disease, mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation, and cardiac insufficiency.

There was a history of indefinite joint pains and frequent sore throats. At the age of 7, a "leaky" heart was diagnosed by the school physician. At 11, symptoms of heart failure were first apparent and became more pronounced, with intervals of slight improvement, until death two years later. The occurrence of occasional fever and moderate leukocytosis was taken to indicate the persistence of an active subacute rheumatic process in the heart. He was under continuous

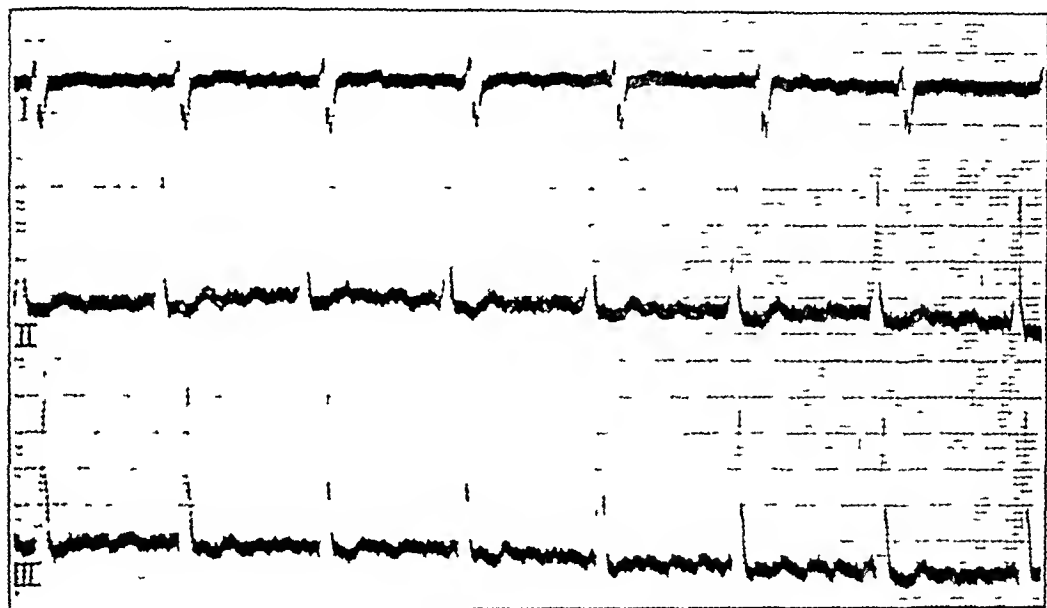


Fig. 3 (case 2)—Leads I, II and III, showing regular ventricular rhythm with rate of 78. In Leads II and III a 5 to 1 ratio is suggested between auricular (f) waves and the ventricular complexes. This would make the rate of the circus in the auricles 390 per minute.

observation in hospital and dispensary from July, 1920, to August, 1924. Fibrillation of the auricles was first noted July 3, 1922, and persisted to the end. No necropsy was performed.

Although more than fifty electrocardiograms were made, regular ventricular rhythm was observed on but six occasions (table 3). In one of these records, the regularity of the interventricular intervals was at times disturbed by shorter or longer pauses between beats (table 4).

CASE 3—L. R., a boy, aged 11 years, admitted for the second time, May 26, 1925, was discharged, improved, August 13. The diagnosis was subacute rheumatic fever, cardiac hypertrophy, chronic cardiac valvular disease, mitral stenosis and insufficiency, adherent pericardium, auricular fibrillation, and cardiac insufficiency.

The boy was first admitted to the hospital, Dec. 22, 1924, complaining of shortness of breath and swelling of the abdomen. At 7, he had rheumatic fever. Dyspnea, which began at the time of the rheumatic attack, was so marked for two years that he was unable to attend school. In 1924, the heart was found to be enormously enlarged. While under observation and receiving digitalis, the

rhythm, which was regular on admission, changed first to auricular flutter, then to auricular fibrillation. The latter irregularity persisted during the time of subsequent observation.

On admission for the second time, there were signs of advanced heart failure. Orthopnea was extreme and there was general anasarca. He had been taking approximately 2 cc of tincture of digitalis daily for a number of weeks, and this dosage was continued during the first two weeks of his hospital stay, during which the periods of regular ventricular rhythm were noted (tables 5 and 6). There were spikes of irregular fever, the temperature at times rising to 101.8. These febrile exacerbations were regarded as of rheumatic origin. It is worthy of note that at the time of regular ventricular rhythm one of the febrile episodes

TABLE 3—Case 2—*I W*, Aged 13

Date, 1922	Electro- cardio- gram	Digitalis	Ventricular Rhythm	Ventricular Rate	T Wave			Remarks
					I	II	III	
July 29	3982	2 cc of tincture daily for preceding 3 weeks	Regular	78	+	±	±	Temperature, 100, bedside notes, "cardiac rhythm is perfectly regular this morning"
September 7	4061	11 Gm of digitalin during preceding 4 days	Regular	76	+	±	±	Temperature, 100
September 8	1069	None	Regular + irregular	66-70	+	+	+	Temperature 100.6 irregular rhythm had more rapid rate
October 25	4179	0.1-0.2 Gm digitalin once a day for preceding 2 weeks	Regular	71	+	±	±	Temperature, 102, pain in arm nauseated
November 27	4268	0.1 Gm digitalin once a day for 10 days preceding	Regular	71	+	±	±	Temperature, 100.2, day before patient noticed that he felt "suddenly unusually comfortable", the regular rhythm lasted about 36 hours, patient awoke during night of November 27 from a nightmare and was again aware of cardiac irregularity
December 29	4404	0.1-0.2 Gm digitalin once a day for 2 weeks preceding	Regular	74	±	±	±	Temperature, 99.6, while playing cards, patient noticed that heart rhythm became regular, it remained so for 3 days

was taking place. The leukocytes at this time ranged from 12,000 to 17,000 and there was a moderate degree of anemia. There were at no time any evidences of digitalis intoxication.

Four months after leaving the hospital, the boy was alive but again having symptoms of advanced heart failure.

CASE 4—*M M*, a woman, aged 48, was admitted Aug 15, 1924, and discharged, improved December 20. The diagnosis was cardiac hypertrophy, chronic cardiac valvular disease, mitral stenosis and insufficiency, auricular fibrillation, and cardiac insufficiency.

No history of rheumatic fever was obtained, although the patient had frequent sore throats in childhood. For many years she noted palpitation on exertion or excitement. Dyspnea and weakness appeared three years before admission, night

outpatient department, Nov 19, 1925 At this time she was free of edema and able to walk a block or two without discomfort She was taking digitalis tincture, 20 drops daily An electrocardiogram showed auricular fibrillation with ventricular rate of 52, the rhythm of the ventricles being totally irregular

COMMENT

A search of the literature has revealed but fifteen cases similar to the four here presented Mackenzie,¹ with his customary clinical acumen, was the first to sense the unusual, which he described as follows

In a case recently under observation the rate under digitalis fell from 110 to 70 beats per minute Prior to the administration of digitalis the rhythm was very irregular, but when the rate fell to 70 beats per minute it was quite regular The patient had no jugular pulse, but by the electrocardiograph Lewis demonstrated that auricular fibrillation was present

TABLE 5—Case 3—*L. R., Aged 11*

Date 1925	Electro cardio gram	Digitalis (Tincture) 2 cc once a day for weeks	Ventric ular Rhythm	Ventric ular Rate	T Wave			Remarks
					I	II	III	
May 27 28 May 29 May 30-June 11 June 12	7939 8008	2 cc once a day 2 cc 2 cc once a day 2 cc	Irregular Regular	80 64	+ +	- -	- -	Taking 2 cc tincture digitalis daily for several weeks prior to admis sion on May 26 Temperature, 101.6, white blood cells, 17,200, bedside notes on this date state "for the last few days the heart has been regular", marked anemia
June 13	8022	2 cc	Regular + Irregular	60	+	-	-	Temperature, 100.4

In the group collected in table 8 age and sex apparently played no rôle as determining factors In nine of the nineteen cases the heart lesions were considered to be rheumatic in origin, in one, syphilitic, seven were presumably due to degenerative processes incident to advancing years, and in two the etiology was not mentioned All of my own patients had rheumatic mitral and aortic disease, enlarged and badly damaged hearts and sufficient elevation of temperature to suggest that an active, acute or subacute rheumatic infection was present The ventricular rates in the nineteen cases ranged from 56 to 90, the average being 68.6 per minute Eight patients died within twenty months of the time of observation, six of these within three months All suffered from advanced heart failure The duration of regular rhythm, so far as was known was from a few hours to a number of days All of the

1 Mackenzie J Auricular Fibrillation, Brit M J 2 872 (Oct 14) 1911

patients were receiving digitalis, a majority of them in full therapeutic doses

Two possible explanations of the mechanism naturally suggest themselves. The first assumes complete auriculoventricular dissociation, the regular beating of the ventricles being initiated by a pacemaker situated at or in the vicinity of the A-V node. The fact that all the patients received digitalis lends some weight to the concept that heart block was present. As pointed out by Lewis,² the intrinsic ventricular rhythm is especially fast when heart block has been induced by digitalis. In his

TABLE 6—Case 3—*Inter-ventricular Intervals (Seconds)*

	Electrocardiogram 8008	Electrocardiogram 8022
	Rate 64	Rate 60
	0.90	1.00*
	0.91	0.99
	0.91	0.97
	0.89	0.98
	0.90	0.98
	0.90	0.99
	0.92	0.96
	0.91	0.97
	0.91	0.99
	0.91	0.96
	0.90	0.95
	0.92	0.96
	0.92	0.98
	0.88	0.96
	0.90	0.97
	0.90	1.00*
	0.90	1.00*
	0.89	0.95
	0.90	0.96
Maximum variation	0.90	
(seconds) exclusive	0.91	
of those marked		
with asterisk ()	0.01	0.04

opinion this condition was present in his own case, of which the electrocardiogram is reproduced in a recent issue of his book.³

An analogous series of twelve cases of complete A-V dissociation, with the auricles contracting normally and with ventricular rates in excess of 60 has been compiled by Hewlett.⁴ A majority of these also were ascribed to the depression of A-V conduction by digitalis. In all, the disturbance was transient or intermittent.

2 Lewis, T. Observations Upon Disorders of the Heart's Action, Heart 3 282, 1911-1912

3 Lewis, T. Clinical Electrocardiography, Ed. 3, Shaw and Sons, 1924, p. 95

4 Hewlett, A. W. A Case Showing Rapid Ventricular Rhythm with Periods of Auriculoventricular Dissociation, Heart 10 9 (April) 1923

TABLE 7—Case 4—*M M*, Aged 48

Date, 1924	Electro- cardio- gram	Digitalis	Ventric- ular Rhythm	Ventric- ular Rate	T Wave			Remarks
					I	II	III	
September 18 to Octo- ber 6		Tincture of digi- talis, 1 2 cc once a day						
October 7	6863		Irreg- ular	62 64	—	±	+	
October 8 to 14		Tincture of digi- talis, 1 2 cc once a day						
October 14	6894	2 cc	Regular + irreg- ular	72 76	—	+	+	Quite comfortable no fever, little or no pulse deficit slight varia- tions in length of cycles in parts of records, during periods of regu- lar ventricular rhythm, rate varies from 72 to 76
October 14 to 19		1 2 cc once a day						
October 20		4 cc						
October 21	6921		Regular + irreg- ular	48 74	—	+	+	Temperature, 99.6 vom- ited later in the day in lead I is shown transi- tion from slower, irreg- ular rhythm to more rapid, regular one slow rate, 48
October 22 to 25		1 cc once a day						
October 25 to 27		None						
October 28	6949		Regular + irreg- ular	60-70				Temperature, 100.6 for relatively long periods there was a series of regular sequences, in- terrupted by occasional irregularity in ventric- ular rhythm the irreg- ular was the slower rhythm, as in previous record

TABLE 8—Case 4—*Interventricular Intervals (Seconds)*

	Electrocardiogram 6894 Rate 72 76	Electrocardiogram 6921 Rate 48-74	Electrocardiogram 6949 Rate 60 70
	0.80	1.47*	0.85
	0.81	0.91*	0.89
	0.80	1.30*	0.85
	0.80	0.79	0.89
	0.70*	0.78	0.87
	0.70*	0.78	0.87
	0.69*	0.78	0.86
	0.81	0.79	0.87
	0.83	0.81	0.87
	0.83	0.81	0.87
	0.83	0.81	0.87
	0.82	0.81	1.28*
	0.83	0.79	1.17*
	0.82	0.79	0.86
	0.82	0.79	0.83
	0.81	0.79	0.84
	0.80	0.79	0.83
	0.84	0.81	0.82
	0.76*	0.79	0.82
	0.97*	0.80	0.83
	0.83	0.79	0.86
	0.79	0.80	0.86
	0.86	0.80	0.85
	0.85	0.80	0.85
	0.82		0.85
	0.83		0.81
	0.82		0.76*
	0.85		0.92*
	0.81		
	0.80		
Maximum variation (seconds) exclusive of those marked with an asterisk (*)	0.91	0.02	0.07

TABLE 9—Summary of Reported Cases of Auricular Fibrillation with Regular Ventricular Rhythm and Rate Over 55

Author	Age	Sex*	Pathology	Clinical Diagnosis	Total Digitalis Given	Ventricular Rate	Remarks
Mackenzie ¹					Full doses	70	Electrocardiogram by Thomas Lewis (not published)
Lewis ²	17	♀	Rheumatism	Mitral stenosis and insufficiency	For 7 days, 40 minims of tincture daily, for one day, 9 minims	80-90	Died on the sixth day after onset of regular rhythm
Leit Dock and Levine ³	78	♂	Rheumatism	Mitral stenosis and insufficiency	Full doses 1.2 Gm in 2 days	75	Three observations, after 1.2 Gm was given, regular rhythm apparently persisted for 4 days, improved
	32	♂				57-73-73	
	52	♂		Chronic myocarditis, chronic nephritis hypertension	5.5 Gm in 65 days	81	Died in 92 days
	72	♂		Chronic myocarditis	2.65 Gm in 10 days	60	Died in 10 months
	65	♂		Chronic myocarditis, hypertension	Tincture, to the point of nausea	85	Improved
	40	♀	Rheumatism	Mitral stenosis and insufficiency	1.7 Gm in 7 days	66	Died in 2 months
	48	♀	Rheumatism	Aortic stenosis	Digitalin, 5 drops, twice a day for 2 months	58	Improved
	72	♂		Chronic myocarditis	2.5 Gm in 6 days	88	Improved
	57	♂		Chronic myocarditis	2.1 Gm in 3 days	56	Died in 14 days
	30	♀	Rheumatism	Mitral stenosis and insufficiency	1.3 Gm in 7 days	68	Died in 21 days
	70	♂		Chronic myocarditis, aortic insufficiency	2.1 Gm in 7 days	75	Two observations, improved
					2.9 Gm in 21 days	75	
	57	♂	Syphilis	Syphilitic aortitis, aortic insufficiency	3.0 Gm in 7 days	58	Improved
	54	♀		Chronic myocarditis	3.85 Gm in 22 days	59	Two observations, improved
					4.45 Gm in 28 days	58	
Levy	16	♀	Rheumatism	Mitral stenosis and insufficiency, aortic insufficiency	None for 6 days until day preceding, when 2 cc of tincture was given	74	Three observations
					3 cc in 2 days	72	
					1 cc in 3 days	70	Died 2 weeks later
	17	♂	Rheumatism	Mitral stenosis and insufficiency, aortic insufficiency	2 cc daily for 3 weeks	78	Six observations
					1.1 Gm during 4 days	76	
					1.1 Gm during 5 days	66-70	Rhythm irregular for short periods
					0.1-0.2 Gm once a day for 2 weeks	71	
					0.1 Gm once a day for 10 days	71	
					0.1-0.2 Gm once a day for 2 weeks	71	Died 20 months later
	48	♀	Rheumatism	Mitral stenosis and insufficiency	1.2 cc of tincture once a day for 4 weeks	72-76	Three observations, always short periods of irregular rhythm, improved
					1.2 cc once a day for 5 weeks	74	
					None for 4 days, before that 1 cc once a day for 1 week	70	Further improvement when seen 1 year later
	11	♂	Rheumatism	Mitral stenosis and insufficiency, adherent pericardium	2 cc once a day for 2 weeks	64	Two observations, improved
					2 cc once a day for 2 weeks	60	Four months later, alive but failing

* In this table, ♂ indicates male, ♀, female

¹ Lea, *P. Lancet* 1 1289, 1915 Other authors are referred to in text

Another interpretation of the regularity of the ventricular contractions in fibrillation is possible in the light of the demonstration that auricular fibrillation, like flutter, is dependent on a circulating wave in the auricles⁵ In fact, fibrillation may be regarded as a variety of flutter, differing from the latter in that the path pursued by the circus is inconstant, its rate of travel is more rapid and the separate circuits are completed in varying times Although in fibrillation coordinate contraction is no longer carried on by the auricles, the ventricles respond to occasional impulses derived from the circulating waves in the auricles The conditions that determine the frequency and degree of regularity of ventricular contractions are not fully understood The rate and path of the circus, the conductivity of the A-V junctional tissues and their state of refractoriness are probable factors concerned

In flutter it is believed that the ventricular response is determined largely by the existing grade of A-V block Thus, there are commonly from 2 to 5 auricular contractions to each ventricular beat, the rhythm of the ventricles being at times regular, at other times irregular Is it not possible that in these cases of fibrillation with regular ventricular rhythm at rates more rapid than are commonly observed in A-V dissociation a condition exists which is analogous to that observed in flutter and that we are dealing with a partial block which, during the periods of ventricular regularity, is constant and at other times varies? The question has, indeed, been raised⁶ and some evidence may be adduced in favor of this view

The amounts of digitalis given in the four cases reported in this article are not usually regarded as sufficient to induce complete heart block Nor do the T waves in the electrocardiograms show changes indicative of full digitalis effect (tables 1, 3, 5 and 7) In several instances, although digitalis therapy was continued after the onset of regular ventricular rhythm, irregularity recurred within a day or two On other occasions, similar or larger doses were given to all of these patients without resultant ventricular regularity The first patient is worthy of special mention in this connection For ten days she had received 0.12 Gm of digitalis daily, then none for six days, then 2 cc of tincture for one day The following morning the ventricular rhythm was regular, the rate 74 In spite of the administration of 1 cc of tincture daily for the next two days, a combination of regular and

⁵ Lewis, T The Nature of Auricular Fibrillation as It Occurs in Patients, *Heart* 8 193 (May) 1921

⁶ Dock, W and Levine, S A The Occurrence of Regular Ventricular Rhythm with a Rate of Over Fifty Cases of Auricular Fibrillation, *Am J M Sc* 167 664 (May) 1924

irregular rhythm was followed on the second day by total arrhythmia. It is interesting but unprofitable to speculate as to the possible effect of active rheumatic lesions on the susceptibility of the junctional tissues.

It is striking that there is no significant variation in the form of the ventricular complexes of the electrocardiograms during periods of regular and irregular rhythm (fig 1). They appear, in fact, to be essentially identical in all of the cases. Such constancy of form points to the uninterrupted supraventricular origin of the impulses giving rise to these complexes and argues against their initiation in the junctional or ventricular tissues during the periods of ventricular regularity.

Complete heart block due to digitalis, once established, ordinarily persists without variation until the action of the drug has worn off. It does not exhibit fluctuations in interventricular intervals, as is evident in some of the curves, measurements of which are given in tables 6 and 8. Case 4 (table 8) is a striking example of the combination of regular and irregular ventricular rhythm, long sequences of absolute regularity being broken by occasional longer interventricular intervals. It suggests partial rather than complete block. In two of the other patients similar combined rhythms were recorded. It is of interest that the irregular rhythm may have either the faster (case 2) or the slower rate (case 4).

A satisfactory demonstration of an absolute ratio between the number of auricular cycles and ventricular beats has not been possible. In leads II and III, figure 2, a 5 to 1 ratio is suggested. This would make the rate of the circus 390 per minute. Curves made with chest leads in case 3 were likewise not conclusive. Atropine tests and vagus or ocular pressure experiments were not done. When tried in several of their cases by Dock and Levine, negative results were obtained in that no change in ventricular rate was observed. In their patients vagus effects apparently did not play a part in controlling the mechanism. Such tests would not necessarily decide the issue with finality since, as Hewlett has emphasized, rhythms arising in the A-V node are very susceptible to vagus influences. Change in ventricular rate following vagal inhibition or stimulation might result whether complete block was or was not present.

Final proof as to the nature of the mechanism has not been brought. The possible analogy to conditions prevailing in flutter is of interest. It is not unlikely that this disorder in rhythm, being transient, occurs more frequently than is commonly recognized.

SUMMARY

1. Four cases of auricular fibrillation have been reported in which the ventricular rhythm showed periods of regularity, the rate of the ventricles being over 60 per minute. Fifteen similar cases have been found in the literature, in which the ventricular rate was over 55

2 The regular ventricular rhythm lasted from a few hours to several days

3 The condition is of diagnostic import in that it may simulate normal (sinus) rhythm

4 The nature of the underlying mechanism has been discussed. Evidence may be adduced in support of the existence of either complete or partial A-V block. The possible analogy to partial block as it occurs in auricular flutter has been pointed out. Final proof of either hypothesis is lacking.

EXTERNAL FACTORS CAUSING VARIABLE RESULTS IN THE KOTTMANN REACTION *

JACOB KASANIN, M D

AND

EMILY KNAPP, A B

BOSTON

Kottmann¹ in 1920 demonstrated a reaction in human blood serum which he asserted varied with the activity of the thyroid. The increased or decreased function of the gland was assumed to affect the protective colloidal properties of the blood serum of the patient and this property, in turn, to affect a certain photochemic reaction of the serum. By means of this, according to his hypothesis, the thyroid activity could be measured.

The technic of the Kottmann reaction is essentially as follows. To 1 cc of fresh unhemolyzed serum in a small Wassermann type test tube, 0.25 cc of 0.5 per cent potassium iodide is added, then 0.3 cc of 0.5 per cent silver nitrate, and the tube shaken after each addition to insure uniform mixing. The tube is then exposed to a 500 watt mazda lamp at a distance of 25 cm for five minutes, at the end of which, 0.5 cc of 0.25 per cent hydroquinone is added with shaking. The color changes are carefully noted at definite time intervals thereafter. In our work we have considered as a delayed reaction one in which no color change could be observed ten minutes after the addition of hydroquinone.

Kottmann's theory of the cause of the differing speeds with which this color development takes place, with different serums, is this. The sensitivity of silver iodide particles to light is proportional to their size, the more finely dispersed their state, the less photosensitive they are, while the coarser the particles, the more sensitive they are. A high protective colloid content or power in the serum, then, might keep the silver iodide in a fine state of dispersion, lessen its photosensitivity, and delay color appearance on the addition of the developer, hydroquinone. A low protective colloid content might conversely allow the formation of coarser particles, with a greater photosensitivity, and so result in a much quicker development of color.

Kottmann found that the serum of a hyperthyroid patient gave a delayed development of color, while a hypothyroid case gave an accelerated reaction, as compared with his group of normal controls.

* From the laboratory of internal medicine in the Boston Psychopathic Hospital.

1 Kottmann, K. Kolloidchemische Untersuchungen über Schilddrüsensprobleme, *Schweiz med Wchnschr* 50 644 (July 22) 1920.

Petersen, H'Doubler and Levinson² in 1922 agreed with Kottmann, finding a delayed reaction in sixty-five out of seventy hyperthyroid cases, and a normal reaction in all but three of 139 normals

Raphael³ worked on psychotic patients without thyroid complication, and found a most remarkable parallel between the affective disorders of a large group of subjects and their Kottmann reactions. He carried out tests at intervals on the same patient during his clinical improvement or progress and obtained a striking agreement between the patient's condition and the Kottmann reaction, in all but eight out of 754 observations on 291 patients

Saunders⁴ reports 400 Kottmann reactions done on psychotic patients, 105 of which show a "delayed" reaction, the time of which he did not give. Of these only one showed any clinical symptoms of hyperthyroidism, while "most of the others had very indefinite symptoms"

Kramer,⁵ using the reaction as an index of thyroid function, obtained unsatisfactory results, getting a retardation of over fifteen minutes in only one out of fourteen cases of hyperthyroidism. In his technic, however, it should be noted that his time for exposure to light is given as fifteen minutes with a 500 candlepower lamp, rather than the five minutes with a 500 watt lamp specified by Kottmann

In our own work we were interested in the possible relation of the Kottmann reaction to the affective states of psychotic patients, as Kottmann and Petersen had observed that fright or excitement in a patient tended to delay the reaction. Single observations were made on seventy patients without thyroid complication according to the technic set forth above. We found that of twenty-three delayed reactions, eleven were from disturbed and excited patients, six from depressed, and six from quiet and cooperative patients. Of forty-seven cases within normal limits or accelerated, there were eleven excited, six depressed and thirty quiet and cooperative patients. From this it may be seen that while the percentage of excited patients is highest in the group showing delayed reactions and of normal patients is highest in the group showing so-called normal reactions, there is no striking consistency, which would show that a delayed reaction is indicative of an emotional state

2 Petersen, W. F., H'Doubler, F. T., and Levinson, S. A. The Kottmann Reaction for Thyroid Activity, *J. A. M. A.* 78:1022 (April 8) 1922

3 Raphael, Theophile, and Smith, G. J. The Kottmann Reaction as Applied to Psychiatric Cases, *Am. J. Psychiat.* 4:161 (Oct.) 1924

4 Saunders, A. M. The Kottmann Reaction in the Insane, *J. Lab. & Clin. Med.* 9:401 (March) 1924

5 Kramer, D. W. The Kottmann Reaction in Thyroid Dysfunction, *Am. J. M. Sc.* 170:75 (July) 1925

We were able to obtain only three definitely hyperthyroid cases, an exophthalmic goiter case with a basal metabolism of plus 95 per cent, a thyrocardiac case with a basal metabolic rate of plus 54 per cent and a case of toxic colloid adenoma of the thyroid. All three showed a normal reaction with beginning color change within five minutes. These cases were obtained through the courtesy of the surgical service of the New England Deaconess Hospital.

We then decided to investigate the technic of the reaction before continuing further with its clinical application. Morse and Fitch⁶ had already stated that preservation of the blood serum tended to accelerate the Kottmann reaction, and this we also found to be true. One of our serums, giving a reaction in which the first color change occurred at the end of fifteen minutes, gave a reaction five hours later in which the first color change was observed at the end of seven minutes. Another serum giving a delayed reaction of one hour gave a reaction within a minute twenty-four hours later. Both serums had stood at room temperature. In addition to this we observed, as did Morse and Fitch, that the first color development began definitely at the surface of the serum.

Morse and Fitch believed that this accelerated action was due, at least in part, to a loss of carbon dioxide from the blood serum. In their experimental evidence, they reported a serum giving a delayed reaction, which when aerated for fifteen minutes gave an accelerated reaction, and which, resaturated with alveolar air, gave the original delayed reaction, with identical times for changes in color. They found also that the acceleration of the reaction was directly proportional to the duration of the aeration of the serum.

With the purpose of investigating further this carbon dioxide factor in the Kottmann reaction, we carried out controlled experiments as follows:

- 1 To confirm the aeration experiments of Morse and Fitch, 1 cc of serum was perfused with air and 1 cc with pure oxygen.
- 2 To study the effect of increased concentration of carbon dioxide, 1 cc of serum was perfused with carbon dioxide.
- 3 To study the effect of increased temperature, 1 cc of serum was heated for a short time in a water bath.

The technic of the experiments was as follows. A sufficient amount of fasting blood was centrifugalized as soon as clotted, and 1 cc of serum added to each of five tubes. A drop of caprylic alcohol was added to each of the five tubes to prevent foaming in the case of those to be

⁶ Morse, Sterne, and Fitch, C. M. The Kottmann Reaction for Thyroid Activity. Carbon Dioxide in the Tested Serum, *J. Lab. & Clin. Med.* 8:692 (July) 1923.

perfused with gas Each perfusion was timed and limited to one minute, the speed of perfusion being regulated so far as possible Carbon dioxide was generated from calcium carbonate and dilute hydrochloric acid in a medium sized Erlenmeyer flask The oxygen was obtained from a tank used for medical work, and the air from a suction blower pump When the temperature factor was being studied, the serums were heated in a water bath at 45-46 C for three minutes, while the control stood at room temperature All tubes were then treated according to the standard technic, the gradations in color being read at the end of five and ten minutes after the addition of hydroquinone The following method of notation was adopted

0 no color change
 ⊕ doubtful
 + faint
 ++ light brown
 +++ brown (reddish)
 ++++ dark brown (chocolate)

From table 1, it may be seen that air and oxygen perfusion for one minute tend to accelerate the reaction, and that the latter is apparently more effective To obtain significant conclusions, however, as to the relative effects of air and pure oxygen on this reaction longer perfusion is necessary

TABLE 1—*Effect of Perfusion of Serums with Oxygen, Air and Carbon Dioxide and of Heating Serums on Kottmann Reaction**

Experiment	Control	Oxygen	Air	Carbon Dioxide	Heat
1	0	++	++	0	0
2	0	+++	++	0	+
3	++	++	++	0	++
4	0	++	+	0	+
5	+	+++	+	+	+++
6	++	++	+++	0	+
7	+	++	++	0	+
8	++	+++	++	0	++++
9	++	+++	+	0	++
10	++	+++	++⊕	0	+++
11	++	+++	—	0	+++
12	++	+++	+++	—	+++
13	++	++++	+++	0	++

* Readings were taken at the end of ten minutes after the addition of hydroquinone

The effect of carbon dioxide introduced into the serum is a striking and almost entirely consistent retardation of the color development In every case but one, the serum gives a distinctly delayed reaction as compared with its control Although no definite time record was kept after ten minutes, most of the carbon dioxide treated serums were observed to show a slight and gradual change in color only after an hour or longer, the controls showed a color change long before, in every case but case 5 In a series of six similar experiments previously performed, we found a delayed reaction in every case

The effect of heating in a water bath for three minutes at 45-46 C in eight cases out of thirteen was a definite acceleration. Since at the increased temperature there would be a loss of carbon dioxide from the serum, this result is the expected one as compared with the delayed reactions obtained after carbon dioxide perfusion. The experiments provide partial confirmation of the suggestion of Morse and Fitch, that carbon dioxide content of the serum or, in other words, the hydrogen ion concentration is an important variable in the Kottmann technic.

We decided to investigate the temperature factor further, lengthening the time of heating. The technic was as follows. A copper water bath large enough to be kept at a temperature between 45 and 46 C for fifteen minutes without difficulty was used. Into the accessory tube rack, tubes containing 1 cc of serum each (obtained in the same manner as before) were placed, and eight minutes later, more tubes, and five minutes later, the last tubes. Three minutes later all tubes were taken out simultaneously, and treated according to the standard technic. We found it most convenient to work with no more than two sets of serums at one time, more than that making accuracy in reading impracticable.

TABLE 2—*Effect of Heating Serums at 45-46 C for Three, Seven and Fifteen Minutes, Respectively**

Experiment	Control (No Heating)	Heating 3 Minutes	7 Minutes	15 Minutes
1	+	++	++⊕	+++
2	⊕	+++	++	++++
3	+	+++⊕	+++⊕	++++
4	+	++	++⊕	++++
5	+	++	⊕	+++
6	+	++	++⊕	+++⊕
7	+	⊕	⊕	++
8	+	⊕	++⊕	—

* Readings were taken five minutes after the addition of hydroquinone.

From table 2 it may be seen that the reaction is consistently accelerated on heating, and that the acceleration is marked after fifteen minutes heating. For lesser periods of heating, however, the acceleration does not always proceed in direct proportion to the length of time of heating the serum. In four of the seven minute serums there is a greater acceleration as compared with the corresponding three minute serums, but in two there is no greater acceleration, and in two there is an actual retardation as compared with the three minute serums, though not with the control. This variability is unmistakable, and we have no explanation to offer except that if the protective colloid power, so called, of the serum is the determining factor in the photosensitivity of the Kottmann serum mixture, and if on heating the serum gradually under-

goes a loss of carbon dioxide with a decreasing hydrogen ion concentration, there may be one or more optimal p_H values in the serum at which this colloid phenomenon takes place

Petersen⁷ states that he found that dog serum that had been for several days in the refrigerator lost its protective power to a "considerable extent," and differed in this respect from serums obtained from patients with hyperthyroidism, these he kept for several weeks with "only a partial loss" of their protective property. We found a definite acceleration in five serums that were allowed to stand for twenty-four hours, at room temperature. In a few experiments in which Kottmann reactions were done on samples of the same serum that had stood at room temperature (table 3) at two hour intervals, we found a general tendency toward an acceleration of the reaction with increased time of exposure to air, but here again as with the heating experiment, a curious inconsistency in the direct proportion of acceleration to time

TABLE 3—*Effect of Exposure of Serums at Room Temperature for Definite Periods of Time**

Experiment	Immediately	2 Hours	4 Hours	6 Hours	8 Hours	24 Hours
1	++	+++	+++⊕	+++	—	+++
2	⊕	++	++	+	—	++++
3	++	0	+++⊕	⊕	—	++++
4	+	+	++	++	—	—
5	0	+	0	0	—	—
6	—+	++	+++	+++⊕	+++⊕	

* Readings were taken at the end of five minutes after the addition of hydroquinone

From the foregoing experiments, however, we feel certain that the p_H of the blood serum is a most important, if not the predominating, factor in the reaction. This factor is so easily varied that the necessary handling of the serums introduces an uncontrollable variable unless the laboratory is elaborately equipped for the purpose. The consistent results obtained by Kottmann, Petersen and Raphael in the differentiation of hyperthyroid cases from normal can only be explained by a control over these variables by a technic that they fail to record in their articles. If hyperthyroidism caused an indefinite delay in color change, as compared with the normal, this p_H factor caused by standing at room temperature and manipulation of the serum would admittedly be of minor significance. The delay in the cases reported by other investigators, if defined at all, has not been long enough to discount, in our opinion, the effects of the p_H variable. Consequently, we believe that the test does not admit of sufficiently accurate reading to be of practical use in the clinical laboratory.

7 Petersen W F, H'Doubler, F T, Levinson, S A, and Laibe, J E F. Studies in the Kottmann Reaction for Thyroid Activity, Arch Int Med 30 386 (Sept) 1922

SUMMARY

1 The Kottmann reaction was performed on serums from seventy psychotic patients and three patients with hyperthyroidism

2 No correlation between the emotional state and the Kottmann reaction was demonstrable

3 In the hyperthyroid cases a normal rather than a delayed reaction was obtained

4 A series of experiments investigating the technic of the Kottmann reaction, especially from the standpoint of carbon dioxide content of the serum, was performed

5 Perfusion of serum with carbon dioxide for one minute causes a striking and consistent retardation of the Kottmann reaction

6 Heating of the serum for fifteen minutes at 45 C causes a striking and consistent acceleration of the reaction

7 Exposure of the serum to room temperature for any length of time causes in general an acceleration of the reaction, exposure for twenty-four hours a striking acceleration

8 The foregoing procedure is equivalent to increasing and decreasing the carbon dioxide content of the serum and consequently varying the hydrogen ion concentration

9 These experiments demonstrate an uncontrollable variable inherent in the technic described by Kottmann and subsequent workers

10 Since the distinction between a normal and a delayed reaction, as reported by various observers up to this time, is not striking or clearly defined, and since we have shown that the p_H variation of the blood serum as manipulated in the reaction is inevitable and sufficient to interfere with conclusions drawn from the reaction, we believe that the Kottmann reaction is of no diagnostic or prognostic significance in the clinical laboratory

WATER METABOLISM

IV SUGAR METABOLISM IN DEHYDRATION *

EDMUND ANDREWS, M D

CHICAGO

The effect on metabolism of varying degrees of hydration has received but little attention. Our metabolic laws have been assumed to apply rigidly and quantitatively, whether the body was supercharged with water or dehydrated to the point of anuria. Such an assumption is theoretically unsound. One would not expect chemical changes to occur with the same results, either quantitatively or qualitatively in solutions of different strengths. Hitherto, investigators have assumed that this was the case and water metabolism has only been studied in relation to edema, acidosis, nephritis, fevers and the general theory of flushing out or diluting toxins. The following experiments show that the problem is deeper and the varying concentration of the tissue fluids produces profound changes in what have previously been regarded as independent metabolic phenomena.

The injection of equivalent amounts of insulin into animals has been expected to bring about a fall in the blood sugar of about the same depth and duration. The following curves will serve as controls for such experiments. Each dog received one half unit of insulin per kilogram of body weight. It will be noted that after a slight transient rise of 5-10 mg., a fall of 10-15 mg. occurs and at the end of about two and one half hours a return to normal has taken place (chart 1).

In order to test the effect on this insulin curve of dehydration dogs were injected with 10 cc. per kilogram of 5 per cent sodium chloride intravenously the day before the experiments. These animals under such stimulus passed about 500 cc. more urine than normal and lost 0.5 Kg. in weight. The concentration of the blood as measured by the refractometer was increased markedly. The fall was quite constant, being about 5-6 degrees in the refractometric index. This loss of fluid is not enough to produce any clinical changes. The dogs showed no evidences of illness and were up and playing about the pen. Temperature changes were not observed during the injections but the temperature was normal when the experiments were made. In other words the degree of dehydration thus brought about was strictly within the limits of ordinary clinical variation. Such animals when injected with equivalent amounts of insulin show a very different reaction. The initial rise in the blood sugar, which is quite constant in the controls,

* From the Surgical Department, University of Illinois College of Medicine

is less or absent entirely. The fall is much more pronounced, averaging about twice as much as in the controls (20 in normals, 40 in dehydrated animals) and the most striking phenomenon in the length of the curve. Thus far in the work none of the animals have been followed for more than eight hours but at the end of that time there is no sign of a return to normal levels (chart 2)

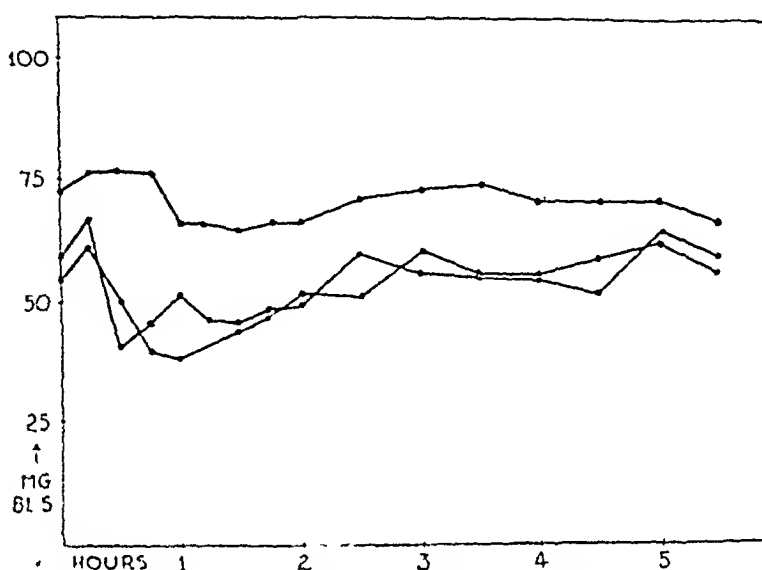


Chart 1—Control insulin curve (one-half unit of insulin per kilogram)

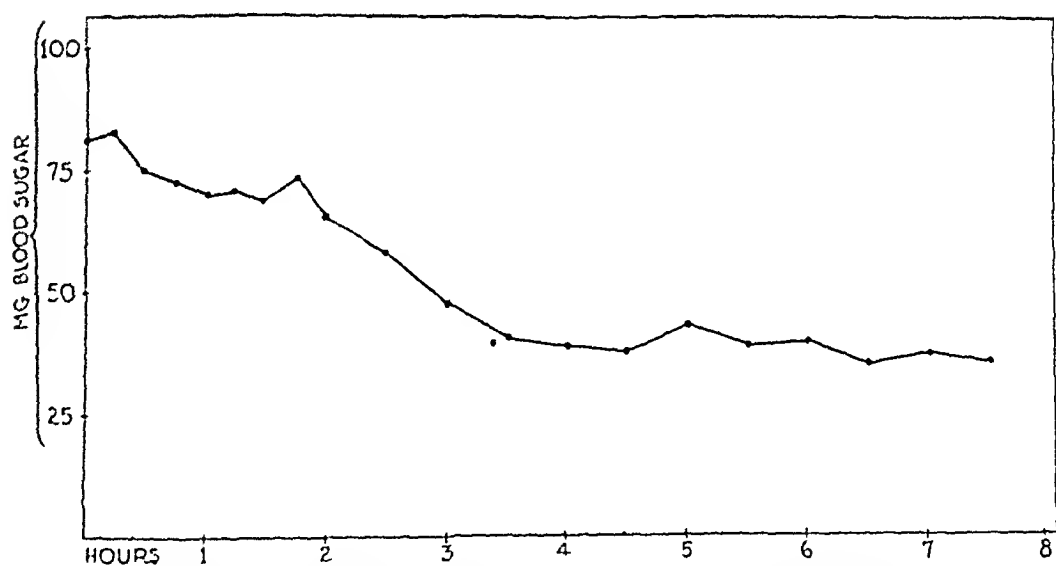


Chart 2—Composite of three insulin curves in dehydration

The question arose at once, "Was it the salt solution which produced these changes?" Therefore the experiments were repeated on animals who were dehydrated by the deprivation of water for forty-eight hours and it is evident from chart 3 that dehydration by either means (hyper-tonic salt or deprivation) yielded quite similar curves

Another possible objection was that these changes in the insulin action might be brought about by acidosis produced by the sodium chloride. This objection is categorically answered by the experiments illustrated by chart 4. Here the animal was flooded with fluids by the administration of 500 cc of physiologic sodium chloride solution intra-

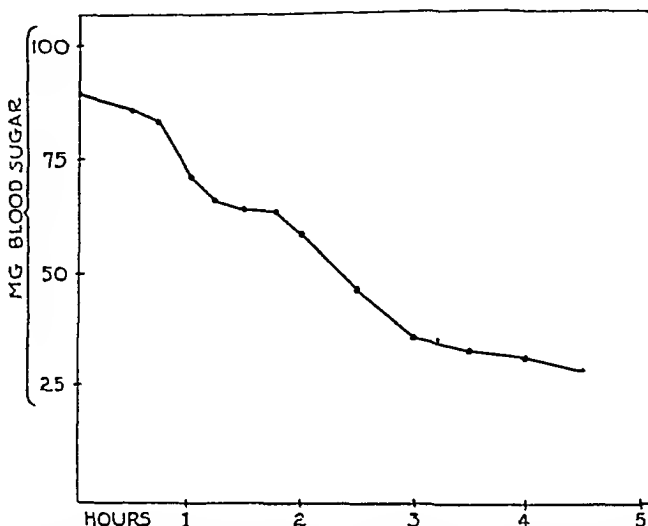


Chart 3—Curve of dog dehydrated by forty-eight hours' deprivation (one-half unit of insulin per kilogram)

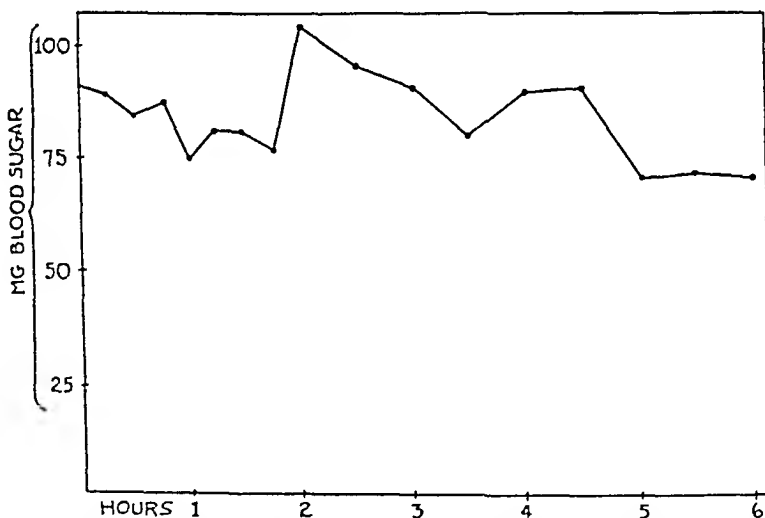


Chart 4—Curve of dog hydrated by intra-abdominal injection of 500 cc of physiologic sodium chloride solution the night before and 300 cc more just before tests (one-half unit of insulin per kilogram)

peritoneally the afternoon before and 300 cc more two hours before the experiment. He received 7.2 Gm of salt as compared to 5.5 Gm for the animal illustrated by curve 2. Therefore, if the acidosis was a factor one would expect the insulin effect to be even greater than in curve 2. Exactly the opposite takes place. In an animal overhydrated, flooded in

water as this one was, the insulin effect is almost abolished. There is a short fall in the blood sugar after which it rises to levels even higher than that at the beginning of the experiment (chart 4)

It is clear, therefore, that the degree of hydration of the tissues is the real factor in these variations. In dehydration the insulin effect is

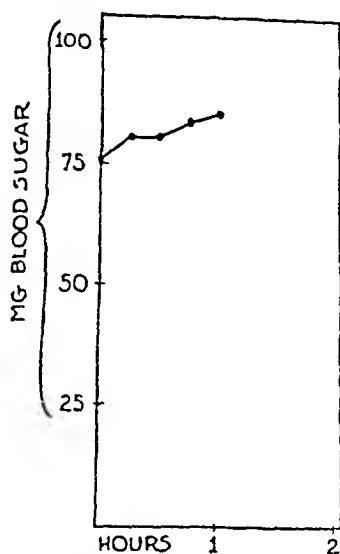


Chart 5—Curve of dog after injection of epinephrine

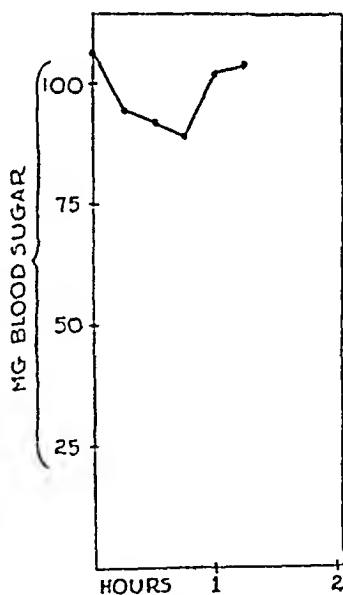


Chart 6—Curve of dehydrated dog after injection of epinephrine

intensified and prolonged and the opposite is true if there is a flooding of the body with fluids

Interpretation of these phenomena is difficult. One cannot state categorically that more or less sugar is burned from such data as the above. Experiments with a gas exchange apparatus are being undertaken to settle this point. However, one would feel much inclined to doubt whether such relatively slight changes in the concentration of

insulin would be capable of producing such changes in its action. If we look a little deeper the question arises as to whether there is any variation in the mobilization of sugar in the body under these conditions. Normally, the injection of insulin not only brings about an oxidation of glucose in the tissues but it also causes a suprarenal stimulation which in turn causes an outpouring of sugar from the liver. As was noted above, in the dehydrated animals there was a lessening or absence of the preliminary rise in the blood sugar on insulin injection, and it therefore was thought possible that when the portal circulation was interfered with this epinephrine action on the liver (sugar mobilization) was interfered with, and that this might account for the length and depth of the insulin curve. In other words, the sugar burned was not replaced so promptly. The following experiments tend to confirm this view.

In apparently normal animals the injection of epinephrine brings about a slight rise in the sugar in the blood (chart 5). In animals who

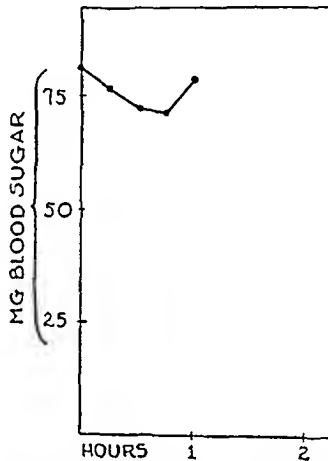


Chart 7—Blood sugar changes caused by injection of epinephrine in patients with portal obstruction due to hepatic cirrhosis

were dehydrated either by injection of hypertonic salt solution or by deprivation of water this epinephrine hyperglycemia does not occur. In fact, there is a gradual lowering of the blood sugar, due in all probability to the using up of larger amounts of fuel by the elevation of general tonus (chart 6). Chart 7 illustrates some experiments further confirming these facts. These are changes in the blood sugar brought about by the injection of epinephrine in patients with portal obstruction due to hepatic cirrhosis. It is evident then that interference with the portal circulation from general dehydration or from portal obstruction will prevent the mobilization of sugar from the liver by epinephrine.

COMMENT

From the foregoing experiments it is evident that our conceptions of sugar metabolism have overlooked an important source of error

Numerous important applications at once suggest themselves. Among the most important I will briefly enumerate the following

- 1 This factor must be considered in the standardization of insulin.
- 2 In postoperative acidosis, the value of fluids is given a rational basis. In the water starved tissues not enough sugar is mobilized from the liver to insure complete oxidation of fats.
- 3 The question of the amount of fluid in diabetic diets is given additional importance.
- 4 The protein sparing action of glucose in wasting disease especially cannot be exerted unless there is sufficient fluid in the body to provide an adequate mobilization of sugar from the liver. In most asthenic individuals, dehydration is marked.

CONCLUSIONS

1 Sugar metabolism, as illustrated by the fall in the blood sugar after administration of insulin, is profoundly influenced by the relative degrees of hydration of animals.

2 The intensity and duration of the fall in blood sugar after administration of insulin are enormously greater in animals who are dehydrated by various means, and much less in animals who are flooded with water.

CORRECTION

Dr Arthur L. Bloomfield, Baltimore, calls attention to two errors occurring in the first formula in the paper by him and Doctor Keefer, "A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man," appearing in the June issue of the *ARCHIVES OF INTERNAL MEDICINE* (p. 822). The formula should read

(1) $\left[\frac{1}{v} \times A \right] - A =$ maximum possible amount of juice secreted in ten minute period, in which

Book Reviews

PHYSIOTHERAPY By HARRY EATON STEWART, M D New York Paul B Hoeber

In the light of advances in the field in recent years, the writer adds to his previous works, "Diathermy and its Application to Pneumonia" and "Physical Reconstruction and Orthopedics", a volume on physiotherapy of fundamental simplicity and thoroughness

Part 1 is a combination of instruction in physics, hospital management and physiology dealing with galvanism, ionization, sinusoidal and galvanic currents, faradism, static, high frequency, phototherapy, actinotherapy, thermotherapy, massage, exercise and hydrotherapy Under each subject the principles involved are discussed in detail, the theoretical application and selection with reference to special conditions, both physiologic and mechanical, are dealt with and the comparative values discussed With each there are careful plans and instructions for installation and use with photographs and plans of methods of application and equipment

Part 2 is clinical with clinical application of the various methods to disease Chapters are devoted to the neuromuscular systems, the bones and joints, the cardiovascular system, the gastro-intestinal tract, the respiratory system, the skin and the genito-urinary system

Especially interesting are the results obtained in diphtheria cases with ultra-violet light, treatment of pyorrhea with quartz lamp and lobar pneumonia with diathermy The results claimed in pneumonia are such that more information regarding diagnosis and controls is required and the results of similar series much be compared before they can be fully accepted The author states that with one exception no patient has been lost who has been treated before the third day The results in hypertension are not convincing of actual benefit

In general, the author believes that the physician will be of greater value to his patient if his knowledge of physiotherapeutic methods permits him either to treat disease himself or to recognize the value in given cases and direct or advise their use A careful study of the book is recommended to everyone

A SYNOPSIS OF MEDICINE Fourth Edition By HENRY LETHEBY TIDY, M A, M D, B Ch, Assistant Physician to St Thomas' Hospital Cloth Price, \$6 Pp 1,000 New York William Wood & Co, 1925

In this synopsis the author strives to present the important principles of medicine in a manner that will enable the reader to grasp rapidly the essential features of any given condition He has thus employed the outline form except in places in which more detailed information seemed necessary The general arrangement of the book is similar to that of Osler's "Principles and Practice of Medicine" In the preparation of the volume, various standard textbooks, systems of medicine and monographs were consulted In the present edition, considerable alterations have been made in the chapters on gallstones and bronchial asthma and in the subject of botulism Visceroptosis, infarction of the lung, purpura and acholuric jaundice are carefully reconsidered New chapters are added on the blood diseases of children and on thrombosis and embolism

The book will satisfactorily serve the purpose for which it was written and thus be useful to the student, the practitioner or the teacher It is, however, not intended to replace the standard textbook and should not be used in this capacity

ARCHIVES OF THE ANDREW TODD MCCLINTOCK MEMORIAL FOUNDATION FOR THE STUDY OF DISEASES OF THE ALIMENTARY CANAL. VOLUME I PLEOMORPHISM IN BACTERIAL PROTOPLASM—A STUDY IN PSITTACOSIS By ANDREW TODD MCCLINTOCK, M D Edited by JOHN WILLIAM DRAPER Privately printed, 1925

The Andrew Todd McClintock Memorial was established by Isabel Cairns McClintock in memory of her husband, who died at the age of 38 of "chronic intestinal invalidism" Several of the productive years of Dr McClintock's life were devoted to a study of the causes of disease of the gastro-intestinal tract and it was his intention to devote the remainder of his life to this study When it was cut short by his untimely death, Mrs McClintock established the memorial in order that further work in his favorite field might be continued in memory of him

The first volume of the archives of this foundation consists in a manuscript that was found among Dr McClintock's papers recording his own investigative work on psittacosis The conclusions drawn by him are in part as follows "An epidemic of disease among parrots occurred in Wilkes-Barre, Pa, March 2, 1917 This was followed by an epidemic among human beings The cause of this epidemic was, originally, the chilling of the parrots, which, by changing the intestinal secretions, affected the generalized bacterial protoplasm in their intestines, so that it assumed powers of disease production in living tissues Energy became extraordinarily heightened, was concentrated, and associated matter, excessively light, was passed upon the surrounding air to human beings It has been developed in this investigation that the type of the local epidemic was due to the general flexibility in the mechanism of character demonstration of the generalized bacterial protoplasm, saprophytic in the parrot intestines The origin of the epidemic depended upon the arousal to an intense activity of that mechanism capable of creating an affinity for animal tissue"

The chief value of this monograph lies not in the work that it records on psittacosis or on pleomorphism in bacterial protoplasm, but in the intimate contact that it gives with the brilliant mind of a medical idealist Here one sees a resourceful and powerful imagination that is balanced and checked by scientific trial and reason The conclusions may be erroneous, but the ideas are delightfully stimulating

THE ART OF MEDICAL TREATMENT By FRANCIS W PALFREY, M D, Visiting Physician, Boston City Hospital, Instructor in Medicine, Harvard University Cloth Price, \$4.50 net Pp 463 Philadelphia W B Saunders Company, 1925

The title of this work is alluring The term "art" in relation to medical practice has been rather loosely used and various meanings have been ascribed to it, to some it may mean technical skill, to others the manner or "approach" of the physician in practice, while to others it may simply mean the ability to maintain the confidence of the patient by any means whatsoever In the introduction Palfrey explains that the "practice of medicine is an art in which the teachings of medical science are put to their practical application", includes not only the therapeutic and diagnostic measures used, but also the manner in which all dealings with the patient are conducted Attempt is here made to include, in addition to therapeutic measures in the narrower sense, something more of the art of medical treatment, by hinting what can be said, either in encouragement, in explanation or in warning to the patient and to his friends The art of medical treatment, therefore, includes both therapeutic measures in the narrower sense and information and mental guidance"

This idea is well carried out in the text The work is similar in many respects to Shattuck's "Principles of Medical Treatment" and is condensed into a small volume It is printed on good paper and the type is excellent, there

are no illustrations. The important infectious diseases and in addition those due to physical agents or poisons, diseases of nutrition and of metabolism and of the various systems of the body are considered. Each disease is discussed under such headings as first thoughts, placing, diet, remedial, supportive and palliative measures, minor care, nursing, information and preventive measures. Several appendices are added on such subjects as stimulation, bed-sores, transfusion, diet and duodenal intubation. These add greatly to the interest and value of the book and are repeatedly referred to in the text.

The book should have a wide field of usefulness for both the student and the general practitioner because the information given is accurate and is clearly and briefly stated and the author displays good sound judgment throughout.

CLINICAL PHYSIOLOGY OF THE STOMACH

SIMULTANEOUS QUANTITATIVE OBSERVATIONS ON GASTRIC SECRETORY VOLUME, ACIDITY AND MOTILITY*

ARTHUR L. BLOOMFIELD, M.D.

AND

CHESTER S. KEEFER, M.D.

BALTIMORE

In a previous article¹ we described a method by which it was possible to estimate the amount of gastric juice secreted and discharged from the stomach in successive ten minute periods following the introduction of a standard stimulus (alcohol). We have now examined a considerable number of people with and without gastric symptoms and the present article deals with some of the data derived from these studies.

THE VOLUME OF GASTRIC JUICE SECRETED BY PEOPLE WITHOUT DIGESTIVE SYMPTOMS

In setting biologic standards it is usually customary to select persons that most nearly approximate normal, and in studying normal gastric function it might at first seem best to study a group of healthy young adults without present symptoms, and with the minimum of past diseases. However, in dealing with patients with digestive symptoms when a diagnostic problem exists, it would be misleading to compare with a supernormal standard, and what one desires to know is the range of variation in people of various ages and of various physical fitness who have no evidence of gastric disease. For this reason the present material comprises a miscellaneous group of people—all ward patients—none of whom, however, had any history or signs of digestive disturbance and all of whom were afebrile, without severe anemia, ambulatory, and in fairly good general condition. A good many members of the group were to all intents and purposes normal people. Thirty patients were studied and the main facts that have been brought out are summarized in the accompanying table.

¹ From the biological division of the medical clinic, Johns Hopkins University Medical Department and Hospital.

1. Bloomfield, A. L., and Keefer, C. S. A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man, *Arch. Int. Med.*, to be published.

Summary of Gastric Examination of Thirty People

Case	Diagnosis	Age	Sex*	Volume of Gastric Secretion in Ten Minute Periods						Highest Acidity Reached During Test, N/10 NaOH	Largest Volume of Stomach Contents During Test	Emptying of Stomach, Time of Minutes	Average Volume of Ten Minute Secretion, Cc	
				Period										
				1	2	3	4	5	6					
54	Bradycardia	50	♂	21.5	20	11	9.5	7		0	64	65	12.5	Convalescent from bronchitis, temperature normal for two weeks
60	Normal	10	♂	16	13	21				93	60	55	23	
62	Normal	14	♂	15	15	42	12	37		57	150	90+	41.5	
60	Normal	19	♂	21.5	16	13	13	11.5	9	43	67	75	11.5	
52	Normal	15	♂	20.5	31.5					95	62	35	29	Entered hospital for septicæmia
51	Normal	15	♂	22	10	10	18.5	16.5	6.5	73	62	65	14	
50	Normal	15	♂	19	14.5	19.5	15	8.5		54	52	75	15.5	
91	Arteriosclerosis, slight hypertension	51	♂	10	12	13	6	5.5		34	48	50	9.5	
96	Convalescent acute nephritis	42	♂	16.5						32	176	20	20	Convalescent from broncho pneumonia
88	Normal	25	♂	34	18	14				42	76	40	22	
110	Psychoneurosis	47	♂	21.5	14	8				118	36	30	19	
116	Normal	49	♂	30.5						35	40	20	20	
124	Normal	23	♂	35	24	16				86	60	40	25	Patient clinically well at time of test
130	Syphilis, perlostitis	14	♂	30	27	15				75	55	50	24	
132	Normal	23	♂	35.5	37.5	35				76	60	50	36	
136	Normal	68	♂	21	13	9	11			71	60	60+	13.5	
138	Normal	34	♂	29	20.5					0	32	30	25	No symptoms at time of test
158	Bradycardia	56	♂	70	66	56				74	125	70+	64	
168	Old stricture of rectum	29	♂	13	11	9	6			0	50	40	10	
176	Hypertension (moderate)	40	♂	27.5	24	18	12	11.5	8	98	64	80	17	
182	Normal	22	♂	23.5	17.5	34.5	32.5	16.5	20.5	20	56	80	24	Well at time of test
188	Gonorrheal arthritis	19	♂	21	13	19	18			57	56	50	18	
196	Normal	28	♂	21	16	20	15	7		100	70	70+	16	
198	Normal	14	♂	27	40	15.5	29.5	17.5		69	64	70	26	
202	Old rheumatic endocarditis	31	♂	18	23					5	30	30	21	No symptoms at time of test
208	Hematuria, unexplained	17	♂	25	56	14				95	86	70+	32	
210	Myocardial insufficiency	40	♂	40	47	14.5				0	84	60+	35.5	
222	Psychoneurosis	27	♂	23	25					15	44	30	24	
228	Angina pectoris	51	♂	23.5	16					0	52	30	20	No symptoms at time of test
230	Dysthyroidism	50	♀	22	15.5	21	23.5	13.5		0	60	60+	19.5	

* In this table, ♂ indicates male, ♀, female

Chart 1 shows graphically the maximum amount of juice secreted in a ten minute period. Each block represents a different case. It appears that twenty-two of the thirty people studied, or 73 per cent, secreted a maximum of from 20 to 40 cc in ten minutes. Chart 2, constructed in a similar way, shows the average secretion of two or more ten minute periods. Here again in about 73 per cent of the cases the amount varied from 10 to 30 cc. In regard to the few persons who secreted the smallest and largest quantities of juice it may be said again

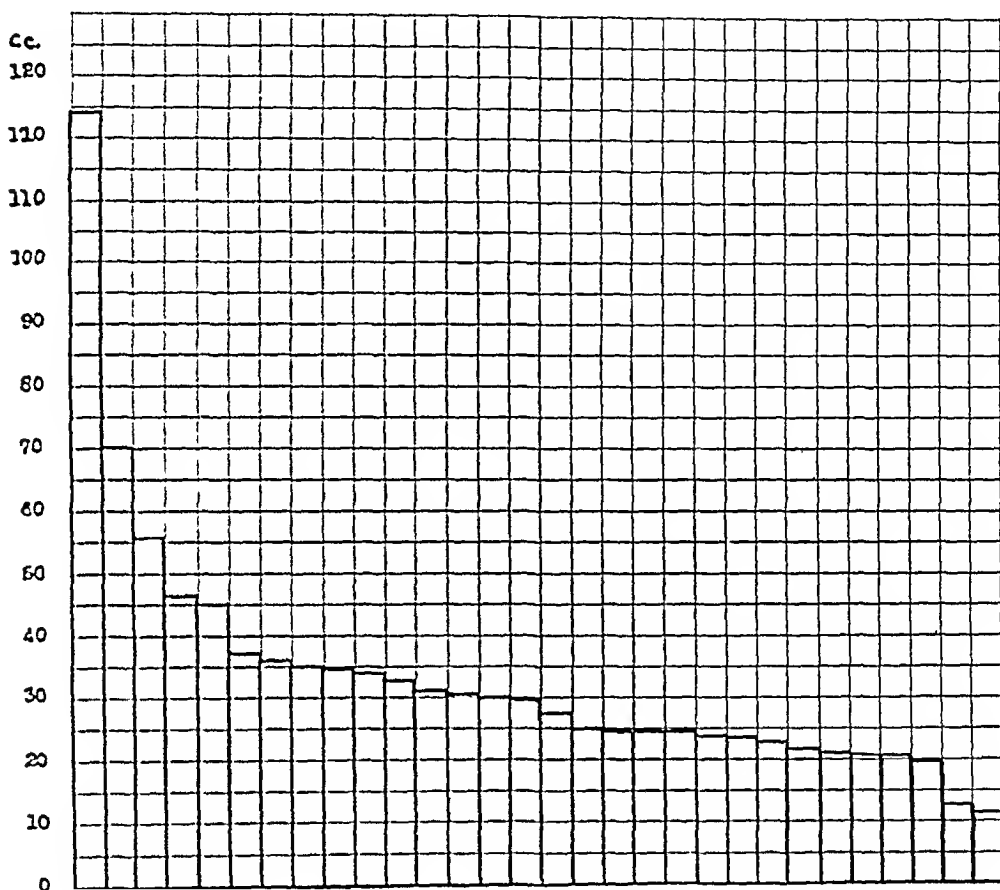


Chart 1—Maximum volume of gastric juice secreted in ten minutes

that they were without digestive symptoms or evidence of gastric disease, and were in no way distinguishable from the major portion of the group.

It appears, therefore, that from 10 to 30 cc represents the usual average ten minute secretion but that in occasional individuals the amount may be larger or smaller.

THE DEGREE OF ACIDITY OF GASTRIC JUICE SECRETED BY PEOPLE WITHOUT DIGESTIVE SYMPTOMS

A great many observations dealing with the acidity of the gastric contents of normal people as determined by plain or fractional test meals

are on record, and the results are usually classified on the familiar basis of hyperacidity, normal acidity, subacidity and anacidity. In Chart 3 is shown the highest acidity (titration with phenolphthalein) of the pure gastric juice reached at any time during the examination of each patient. Each column represents a different person. The striking feature of the chart is the steady graduation from low acidities up to high ones. These observations, together with many others, not here included suggest that it is perhaps unwise to define any rigid standard of normal acidity as the variations are so wide. This point will be discussed further in connection with the diagnostic significance of the gastric secretion.

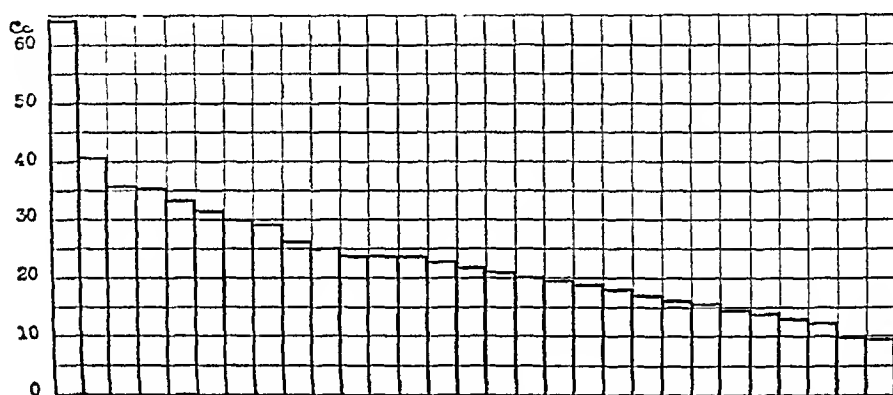


Chart 2—Volume of gastric juice secreted in ten minutes (average of several ten minute periods)

THE RELATION OF THE DEGREE OF ACIDITY TO VOLUME OF GASTRIC JUICE SECRETED

At the beginning of these studies it was suspected that there might be some relationship between the degree of acidity of the gastric juice and the volume secreted. Chart 4, in which maximum secretion per ten minute period is plotted against maximum acidity, shows this not to be the case. With volumes of 25 cc., for example, acidities all the way from 0 to 120 were encountered. It may be seen, too, that the volumes secreted in the anacidity cases varied greatly. After all this is quite comprehensible when the complexity of the whole matter is considered and the various elements of the gastric secretion—mucus, acid and pepsin—which probably are not all produced by the same cells, are taken into account. It may be emphasized that these findings have nothing to do with the fact, which is well known and which we have confirmed, that the acidity may increase in the individual case as volume of secretion increases after stimulation.

GASTRIC MOTILITY IN PEOPLE WITHOUT DIGESTIVE SYMPTOMS

If one takes as a measure of gastric motility the amount of stomach contents which passes the pylorus in a unit of time, it immediately becomes apparent that the same quantity may be ejected under rather diverse conditions. If the pylorus is widely open much material may pass out with few contraction waves, on the other hand, with closure of the pylorus considerable gastric motor activity will be necessary to eject the same amount of material. Furthermore, the matter is complicated by the fact that as the stomach becomes empty secretion usually

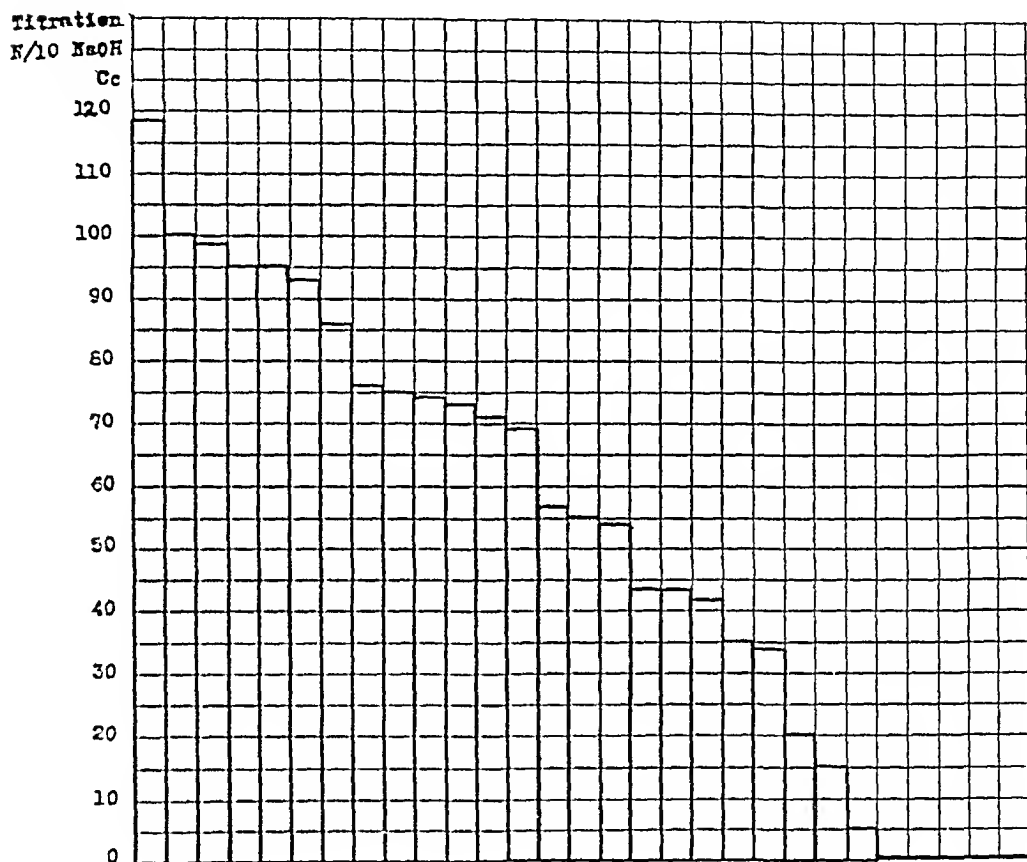


Chart 3—Highest acidity reached in each case (titration with phenolphthalein)

diminishes, the very fact that the pylorus is closed tends to keep up secretion. It seems safer, therefore, to confine the present analysis of gastric motility to a few relatively simple facts.

In each observation a standard quantity of fluid was introduced through the tube into the fasting stomach and by complete aspiration at ten minute intervals it was possible to plot curves of the volume of gastric contents which at any moment consists of the fluid introduced plus the juice secreted less the quantity of material passed out of the stomach or absorbed through its walls. Two types of reaction were noted. In some cases there was an immediate decrease in the volume of

stomach contents This decrease continued until the stomach had emptied itself with greater or less rapidity In other observations there was an increase of volume lasting for a variable length of time and then a decrease In practically every instance, however, the course of the curve was smooth, that is to say there were no rapid or repeated fluctuations from larger to smaller volumes Several representative curves illustrating this point are shown in chart 5

In chart 6 are shown the highest volumes of stomach contents reached during the tests Each column represents a different case It is seen at once that the response to an identical stimulus is very different

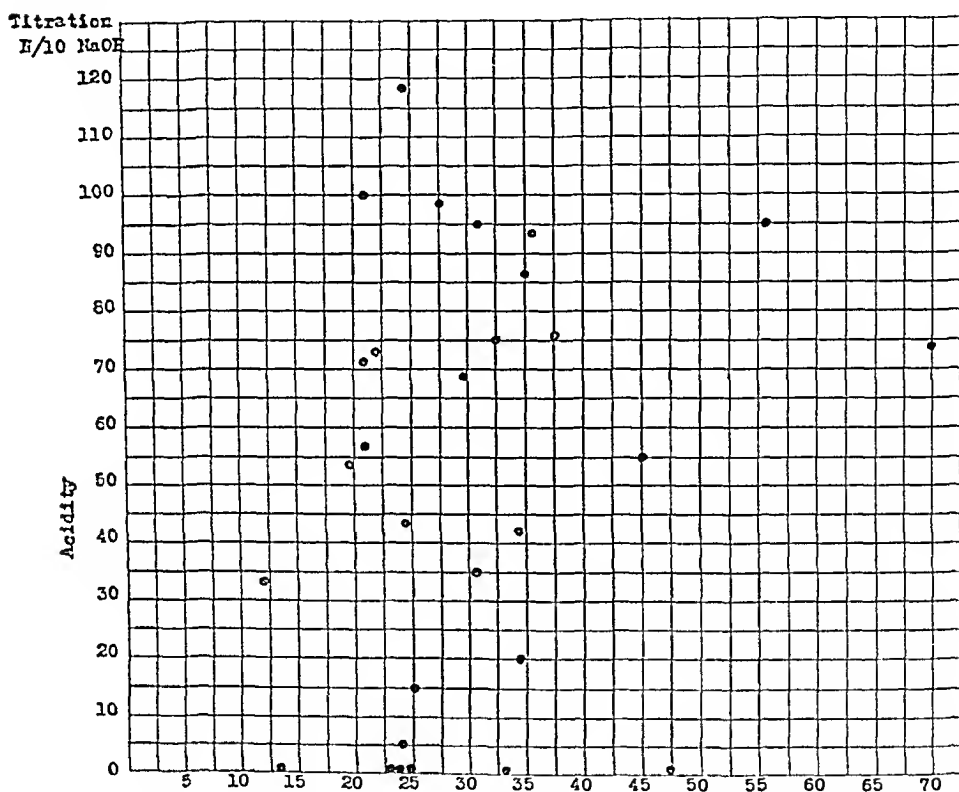


Chart 4—Relation of volume of secretion to acidity in different people

in different observations and two explanations suggest themselves First, a very large secretion of gastric juice may as it were "flood" the stomach so that volume of contents rises, on the other hand, the volume whether large or small might be explained by the readiness with which fluid passes out of the stomach That the second possibility is in the main correct is shown by a further consideration of chart 6 In the lower shaded part of each column is indicated the average volume of juice secreted in ten minutes It is seen that there is no clear relation between this quantity and the total volume of stomach contents Neither does the degree of acidity of the gastric juice seem to have any bearing on the

total contents of the stomach. The dots in chart 6 indicate the maximum titratable acidity in each case and it may be seen that similar volume relations follow in persons whose acidity may vary from 0 to 100. These observations may we believe, be taken as evidence against the theory of acid control of the pylorus, a theory that has been questioned recently by various writers.

If we turn now to the question of gastric motility from the standpoint of the emptying time of the stomach the results of our observations

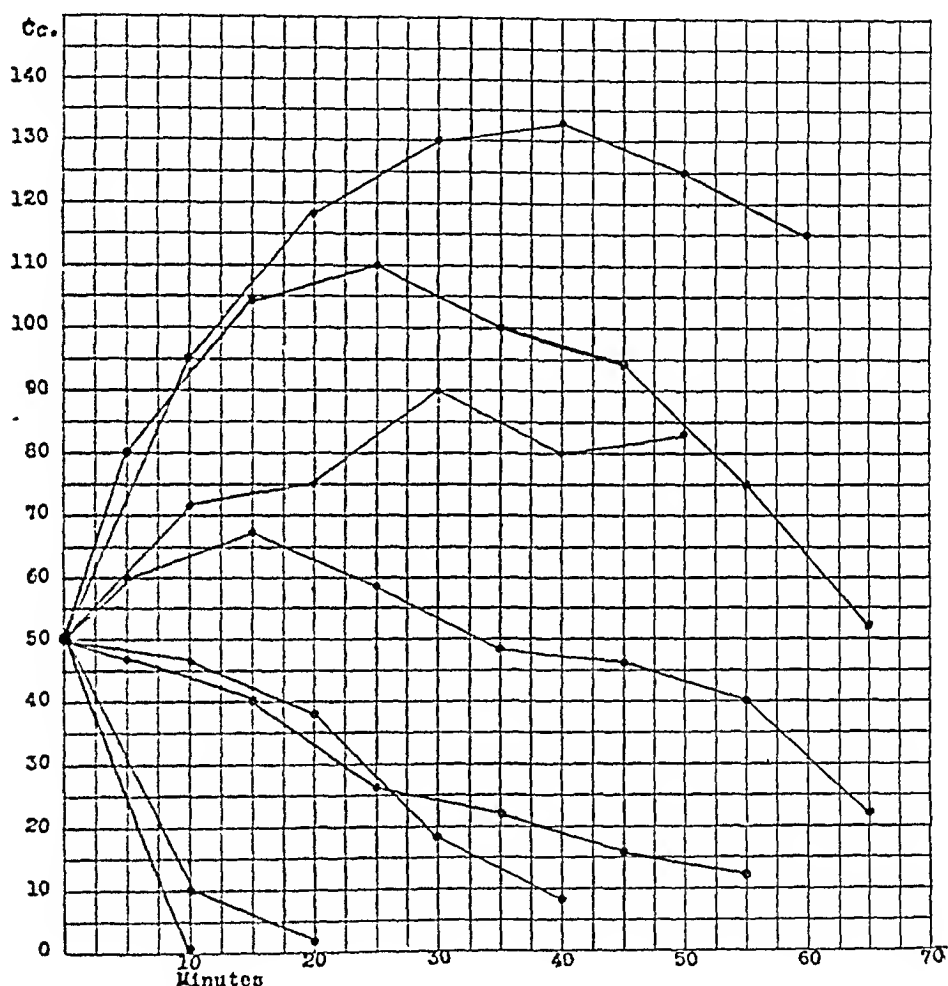


Chart 5—Volume curves of stomach contents in various people (ten minute intervals after a standard meal of 50 cc of 7 per cent alcohol solution)

are shown in chart 7. Each column represents the number of minutes that elapsed after the introduction of the standard 50 cc meal until the stomach was empty (contents 10 cc or less). It is seen that the emptying time under these conditions varied in different people from twenty to over ninety minutes. No correlation with volume of secretion (average for ten minute period—shaded column) or with acidity (dotted line) can be made out.

FINDINGS ON REPEATED EXAMINATIONS OF PEOPLE WITHOUT
DIGESTIVE SYMPTOMS

In order to appreciate changes in gastric functions which result from disease and to evaluate properly the results of treatment, it is necessary to know the range of variation in the same person at various times. A good many observations on repeated tests of gastric acidity by the Ewald meal and the fractional meal are on record. In some instances considerable variation has been reported but the most recently

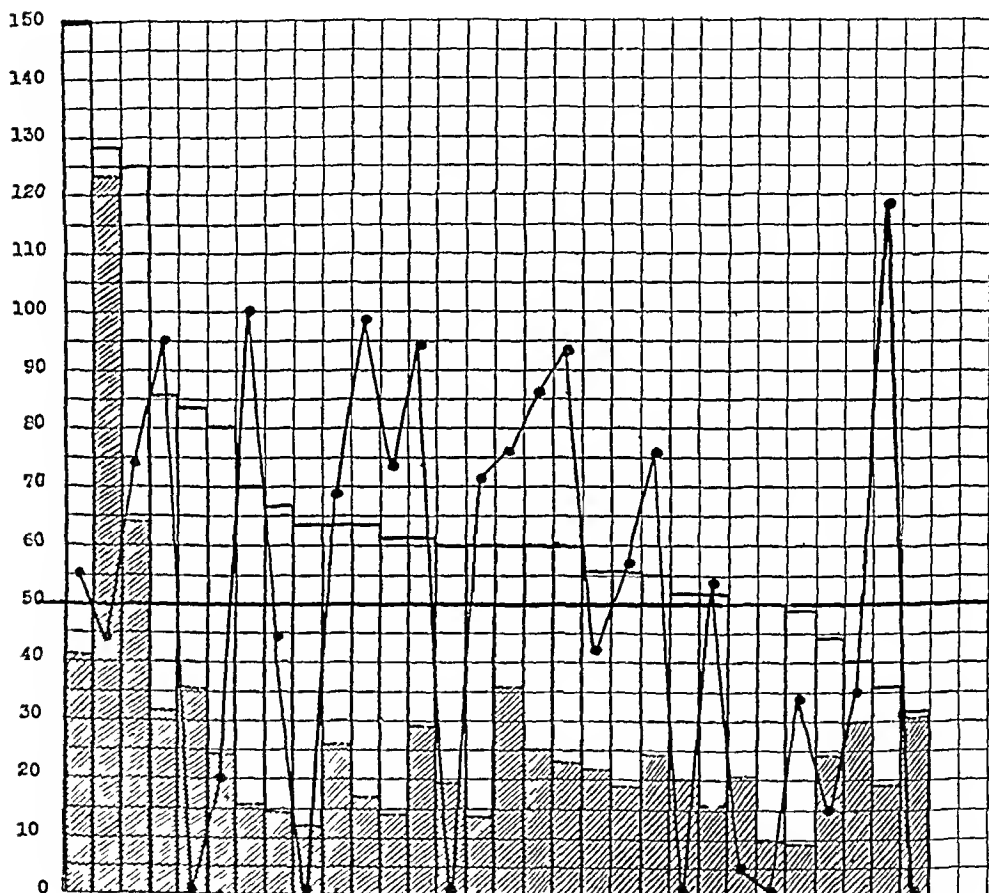


Chart 6—Relation of highest volume of gastric contents (unshaded columns, cubic centimeters) to volume of gastric secretion (shaded columns, cubic centimeters) and acidity (dots titrable acidity)

and carefully controlled examinations seem to indicate that with the fractional meal the same general type of curve is fairly constant in the individual. The literature on this subject is reviewed by Bell and McAdam.²

In the present work the relations of acidity, volume of secretion and motility as found on repeated examinations are analyzed. In sixteen

of our control group repeated examinations were made and in chart 8 are shown the results as regards the maximum titratable acidity which was reached. The dots in each vertical column refer to the acid values in one person, each dot indicating the result of a separate test. The second and third examinations were made after intervals of from one week to several months, but the highest values, regardless of whether they were obtained on the first or on a repeated examination, are charted in the upper curve. It is apparent that the acid values remain remarkably constant, in no instance was there a transition from low acidity to high acidity or vice versa. This is the more significant when it is recalled

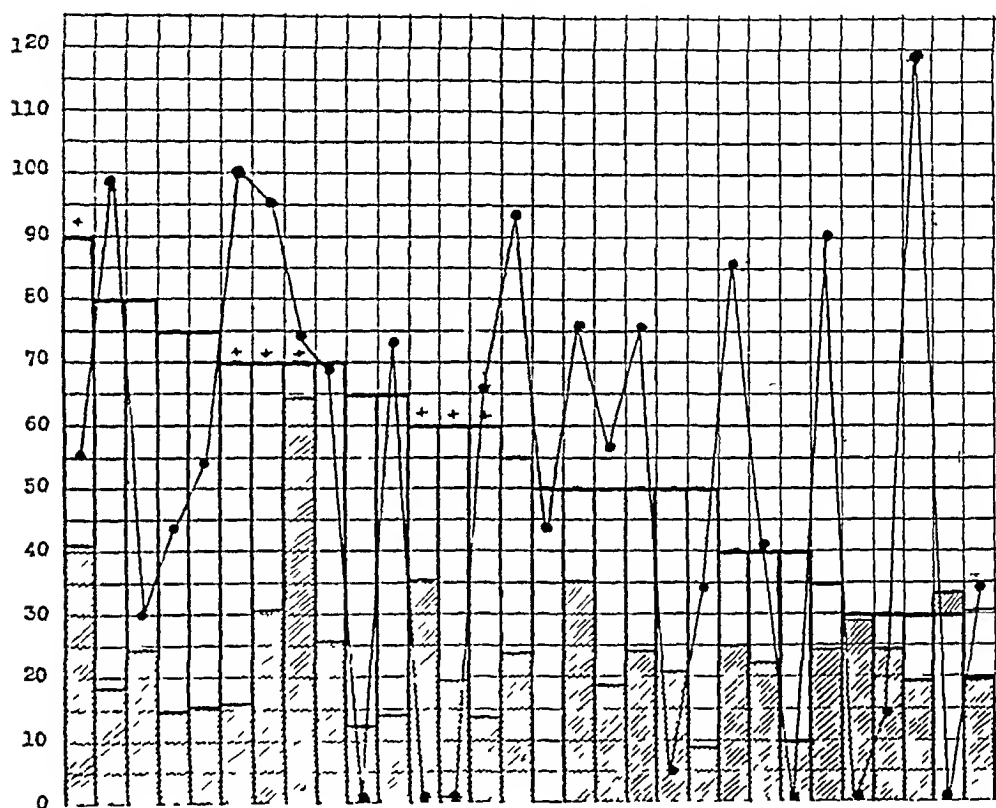


Chart 7—Relation of emptying time of stomach (unshaded columns, minutes) to volume of secretion (shaded columns, cubic centimeters) and acidity (dots titration with tenth normal sodium hydroxide)

that these figures do not refer to acidity of juice as secreted but to the highest acidity attained by the mixed juice in the stomach during the examination, a value which obviously must vary with motility and volume. It would seem therefore, that under uniform conditions of examination a normal person secretes a gastric juice of *highly constant acidity*.

In chart 9 the findings as regards volume of gastric juice secreted on repeated examinations are shown. Each dot represents the number of cubic centimeters of secretion during ten minutes, the value being obtained from an average of the various ten minute periods of the

entire examination. The two dots in each vertical column indicate the results of two tests of the same person. The second test was done within from one week to three months after the first, but the highest value in each case is placed above the lower regardless of sequence of examination. It is seen that the volumes secreted by a particular person are remarkably uniform on successive examinations.

When we turn to the question of motility the findings are quite different. In chart 10 each group of vertical columns represents in cubic centimeters the highest volumes reached in the stomach during repeated tests of the same person. It is seen that in a good many cases

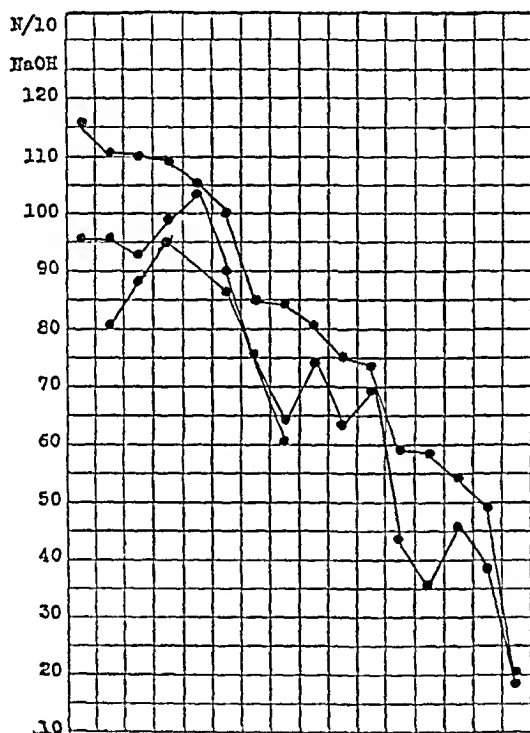


Chart 8—Acidity of gastric juice on repeated examinations of same persons

the results were quite variable. The dots indicate the emptying time in each test. Here even more variation is apparent as illustrated by the cases in which emptying times of ten and of seventy minutes were found on successive occasions.

COMMENT

In the charts we have presented the results of a simultaneous quantitative study of gastric secretion, acidity and motility following a standard stimulus in essentially normal people without digestive symptoms. Two distinct facts are brought out: (1) that the volume of secretion and the degree of acidity vary within considerable limits in different people but under the conditions of these experiments are practically constant.

in the same person on repeated examinations, whereas (2) the motility is extremely variable. There was no relation, in the group between reaction of stomach contents and age, sex, condition, blood count and extra-abdominal disease, to mention only a few of the factors which it is alleged affects gastric acidity. *A priori* there is no reason to believe that all "normal" human beings do or should secrete a gastric juice of

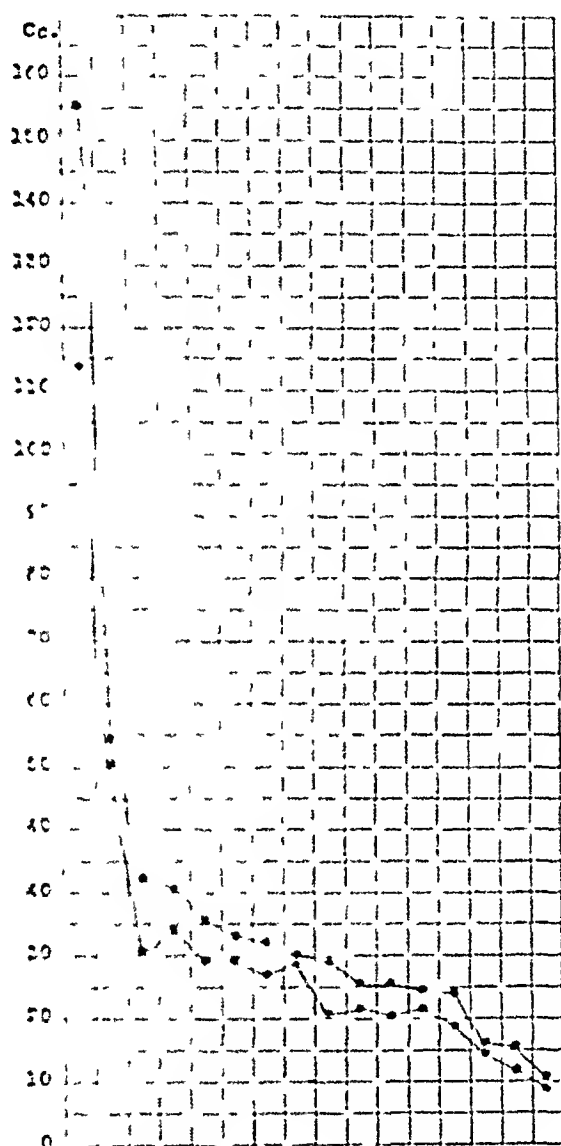


FIGURE 6—Volume of gastric secretion on repeated examination of same persons

uniform composition any more than that they all secrete the same volume and quality of sweat in response to the same stimulus. The demands from the standpoint of regulation of body constants are not at all to be compared with those obtaining in the case, for example, of blood reaction. For the given individual, however, the type of response to a constant gastric stimulus seems quite fixed as regards acidity and volume of secretion. What, if any, factors may alter this individual reaction are

entire examination. The two dots in each vertical column indicate the results of two tests of the same person. The second test was done within from one week to three months after the first, but the highest value in each case is placed above the lower regardless of sequence of examination. It is seen that the volumes secreted by a particular person are remarkably uniform on successive examinations.

When we turn to the question of motility the findings are quite different. In chart 10 each group of vertical columns represents in cubic centimeters the highest volumes reached in the stomach during repeated tests of the same person. It is seen that in a good many cases

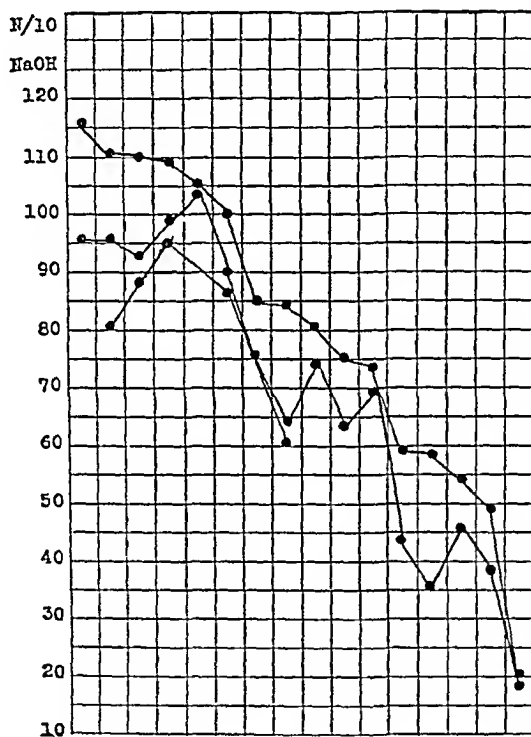


Chart 8—Acidity of gastric juice on repeated examinations of same persons

the results were quite variable. The dots indicate the emptying time in each test. Here even more variation is apparent as illustrated by the cases in which emptying times of ten and of seventy minutes were found on successive occasions.

COMMENT

In the charts we have presented the results of a simultaneous quantitative study of gastric secretion, acidity and motility following a standard stimulus in essentially normal people without digestive symptoms. Two distinct facts are brought out: (1) that the volume of secretion and the degree of acidity vary within considerable limits in different people but under the conditions of these experiments are practically constant.

in the same person on repeated examinations, whereas (2) the motility is extremely variable. There was no relation, in the group between reaction of stomach contents and age, sex, condition, blood count and extra-abdominal disease, to mention only a few of the factors which it is alleged affects gastric acidity. *A priori* there is no reason to believe that all "normal" human beings do or should secrete a gastric juice of

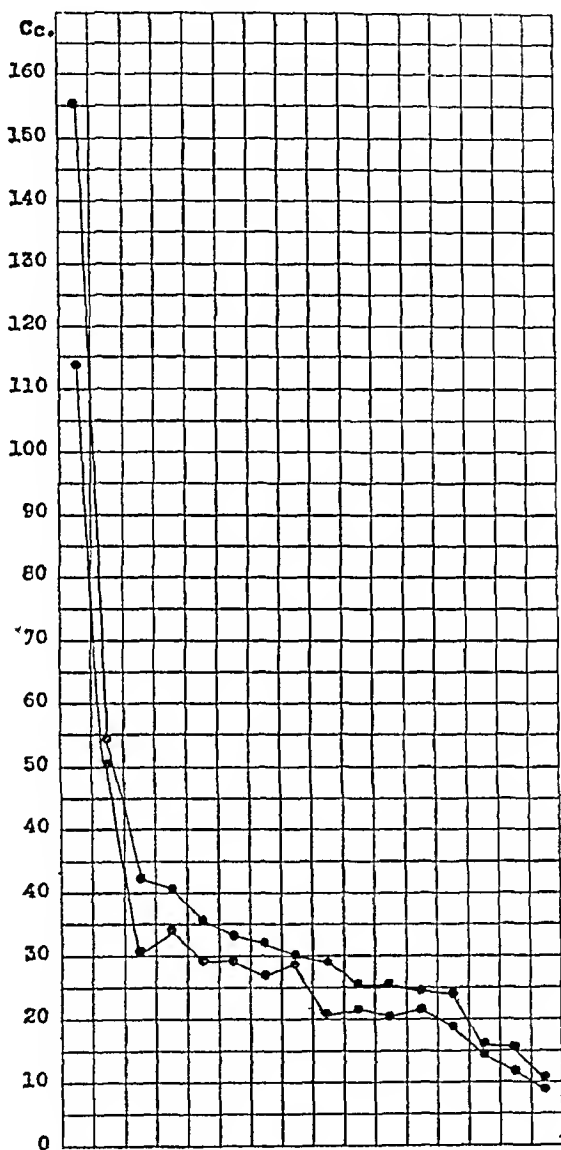


Chart 9—Volume of gastric secretion on repeated examination of same persons

uniform composition any more than that they all secrete the same volume and quality of sweat in response to the same stimulus. The demands from the standpoint of regulation of body constants are not at all to be compared with those obtaining in the case, for example, of blood reaction. For the given individual, however, the type of response to a constant gastric stimulus seems quite fixed as regards acidity and volume of secretion. What, if any, factors may alter this individual reaction are

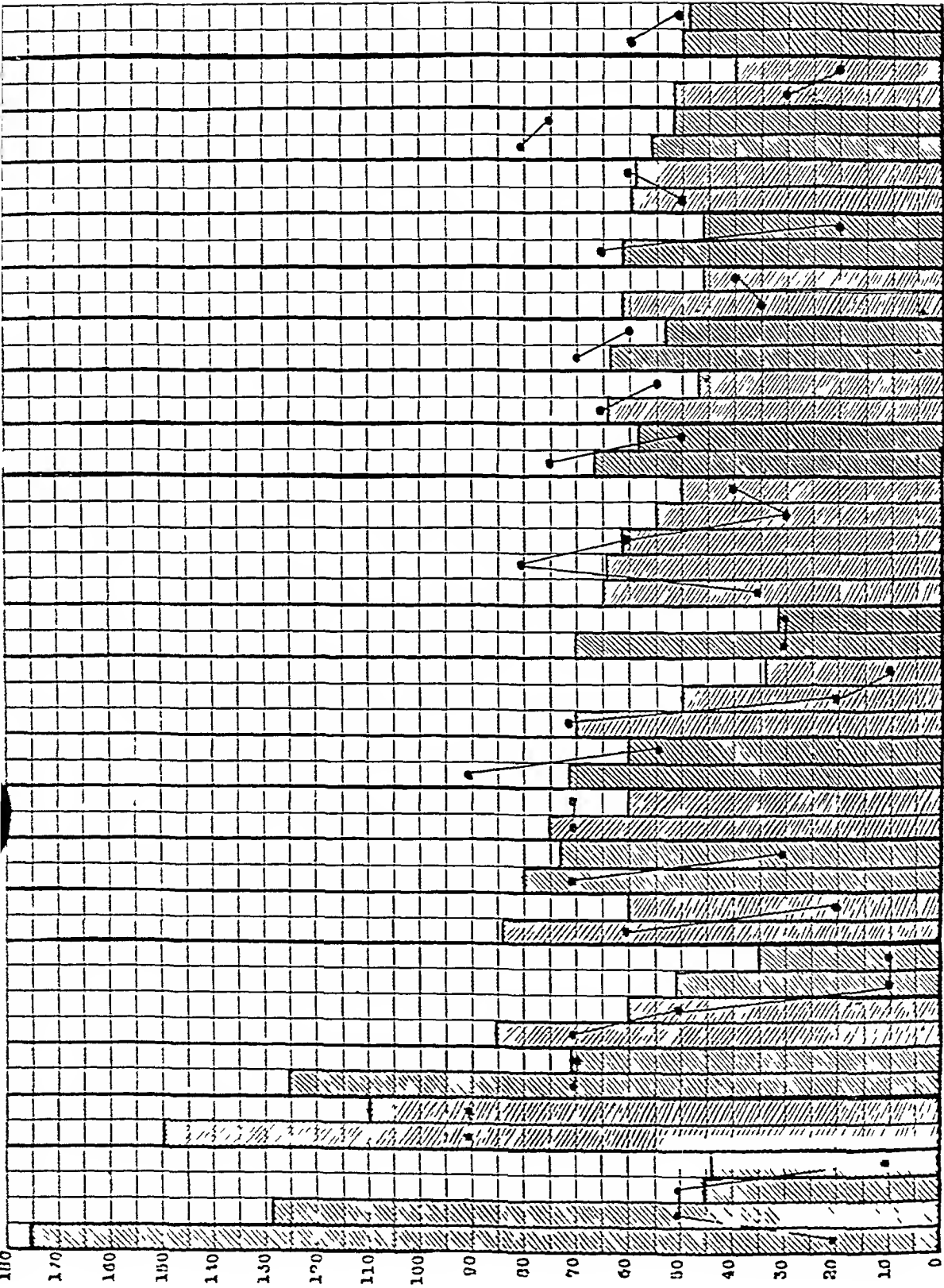


Chart 10—Motility on repeated examinations of 41 people, each group of columns (cubic centimeters) represents highest volume reached in stomach on successive tests of one person, dots represent employing time (minutes)

not yet clearly known. Anatomic disease of the stomach (carcinoma, severe gastritis, etc.) probably does, but it seems equally clear that minor extra-abdominal disorders do not. One may raise the question, too, of whether the terms hypernormal, normal, hyponormal and hyperacidity are satisfactory as they have clinical implications that do not appear altogether warranted. It might be better to speak simply of low, average and relatively high acidities. One may emphasize, too, the absence of any definite relation between volume of secretion and acidity.

Motility, on the other hand, was found in this group to be very variable. The same individual may empty his stomach within a few minutes on one occasion and later accumulate a large volume of gastric contents which is discharged only after a long interval. This question will be more fully discussed in another article.

CONCLUSIONS

1 The volume of gastric juice secreted by people without digestive symptoms in response to a standard stimulus varied between 9 and 69 cc for a ten minute period.

2 Seventy-three per cent of the group secreted from 10 to 30 cc in a ten minute period.

3 Highest acidity of the gastric contents (titratable) varied from 0 to 118. All degrees between these extremes were encountered.

4 No relation was found between volume of juice secreted and acidity.

5 The motility of the stomach in different people varied widely and bore no relation to volume of secretion or to acidity.

6 On repeated examinations of the same person acidity and volume of secretion were practically constant, motility varied greatly.

HYPERTENSION AND CONSTIPATION

A STATISTICAL INQUIRY *

WALTER C ALVAREZ, M D

R L McCALLA, M D

AND

A ZIMMERMANN, D R E S S C

SAN FRANCISCO

It is commonly assumed by practicing physicians that "intestinal autointoxication" has something to do with the production of hypertension. The more thoughtful writers on the subject, knowing that there is no mass of statistics to which they can turn for enlightenment, are guarded in their statements, but those who live by washing colons, and those who have for sale laxative drugs and foods and patented syringes have no such inhibitions. They proclaim from the housetops that one of the dire consequences of constipation is high blood pressure, and to a large extent their propaganda is believed.

It seemed wise, therefore, to study the problem statistically, that is, to compare the pressures of several hundred men and women with normal bowels with those of several hundred constipated individuals. It is really hard to understand why, during the course of years of argument on the subject, so simple a thing has not been done.

In this study we have analyzed the records of 410 men and 585 women, office patients of one of us (W C A). Of these, 436 were classed as normal, 414 as habitually constipated, 110 as having occasional or recent constipation, and thirty-five as having diarrhea.

We have analyzed separately the data from men and women, because their standards of pressure are quite different. We have also had to take into account the age and weight distributions of the various groups in order to make the necessary corrections in the averages that we present here. Without such corrections our results might be misleading because we cannot offhand compare the mean pressures in any two groups. If one group should happen to be made up largely of young, thin persons and the other mainly of old, stout persons, other things being equal, the second group would have to have a much higher average pressure than the first. To be sure we ordinarily do not meet with such extreme disparities in the age and weight composition of groups, but the disparities that we do regularly encounter not infrequently account for all the difference that we get between two uncorrected means.

* From the George Williams Hooper Foundation for Medical Research and the Department of Medicine, University of California Medical School.

The method of making the correction in data from women has been described in a recent article by Alvarez and Zimmermann¹ In this article we supply the necessary standards for the age and weight correction in men These standards unfortunately are based on a rather small group, but so far as we know, they are the only ones yet available for our purpose The figures prepared by the insurance companies do

TABLE 1—*Blood Pressure in Men, by Age Groups, Standards for the Age Correction*

Blood Pressure	Age									
	16 to 29		30 to 39		40 to 49		50+		All Ages	
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent
From 90 to 94			1	0.8	1	0.9	1	0.9	3	0.7
95 to 99	1	1.5	1	0.8	1	0.9	2	1.8	5	1.2
100 to 104	2	3.0	3	2.3	3	2.6			8	1.9
105 to 109	5	7.5	5	3.8	3	2.6	3	2.7	16	3.8
110 to 114	4	6.0	10	7.5	6	5.3	5	4.5	25	5.9
115 to 119	7	10.4	13	9.8	10	8.8	8	7.3	38	9.0
120 to 124	11	16.4	18	13.5	11	9.6	11	10.0	51	12.0
125 to 129	5	7.5	20	15.0	14	12.3	3	2.7	42	9.9
130 to 134	7	10.4	17	12.8	19	16.6	11	10.0	54	12.7
135 to 139	6	9.0	12	9.0	8	7.0	6	5.4	32	7.6
140 to 144	7	10.4	10	7.5	12	10.5	11	10.0	40	9.5
145 to 149	8	11.9	5	3.8	7	6.1	5	4.5	25	5.9
150 to 154	1	1.5	8	6.0	6	5.3	8	7.3	23	5.4
155 to 159	1	1.5	4	3.0	2	1.8	5	4.5	12	2.8
160 to 164			2	1.5	5	4.4	12	10.9	19	4.5
165 to 169			3	2.3	2	1.7	4	3.6	9	2.1
170 to 174	1	1.5			1	0.9	2	1.8	4	0.9
175 to 179					1	0.9	4	3.6	5	1.2
180 to 184					1	0.9	1		2	0.5
185 to 189					1	0.9	3	2.7	4	0.9
190 to 194	1	1.5					1	0.9	2	0.5
195 to 199							1	0.9	1	0.2
200 to 204										
205 to 209							1	0.9	1	0.2
210 to 214										
215 to 219							1	0.9	1	0.2
220 to 224										
225 to 229										
230 to 234							1	0.9	1	0.2
235 to 239										
240 to 244			1	0.8					1	0.2
245 to 249										
Total	67	15.8	133	31.4	114	27.0	110	25.8	424	
Mean		129.4		130.5		133.4		144.1		134.7
S. D.		16.8		17.9		17.8		25.7		21.0
P. E. of mean		1.4		1.0		1.1		1.7		0.7

not help us because they are based only on accepted cases and not on the population as we find it

As a description of the arithmetic used in getting the correction factors makes almost unintelligible reading, we must ask the inquiring student to consult the article mentioned The basic principles underlying the process will be found in chapter 9 of Pearl's "Medical Biometry and Statistics"

1 Alvarez, W. C., and Zimmermann, A. Blood Pressure in Women as Influenced by the Sexual Organs, Arch Int Med 37 597 (May) 1926

BLOOD PRESSURE STANDARDS IN MEN

Table 1 shows a few interesting things. We notice that the averages for the four age groups are 129.4 ± 1.4 , 130.5 ± 1.0 , 133.4 ± 1.1 , and 144.1 ± 1.7 . These findings agree with those made on university students² in showing that the blood pressure does not rise in men up to the age of 40 and little up to the age of 50. The definite rise comes after 50. It is of interest to compare these averages with those found in women,

TABLE 2—*Blood Pressure in Men, Standards for the Weight Correction, All Ages*

Blood Pressure	Build					
	Thin		Normal		Stout	
	F	Per Cent	F	Per Cent	F	Per Cent
From 90 to 94	3	3.5				
95 to 99	1	1.1	4	1.6		
100 to 104	3	3.5	6	2.3		
105 to 109	5	5.7	10	3.9		
110 to 114	9	10.3	15	5.8	1	1.7
115 to 119	16	18.4	23	9.0	2	2.4
120 to 124	15	17.3	32	12.5	6	7.1
125 to 129	7	8.0	29	11.3	8	9.4
130 to 134	9	10.3	31	12.1	16	18.8
135 to 139	1	1.1	23	9.0	7	8.2
140 to 144	6	6.9	27	10.5	6	7.1
145 to 149	3	3.5	14	5.5	6	7.1
150 to 154	2	2.3	10	3.9	11	13.0
155 to 159	1	1.1	9	3.5	4	4.7
160 to 164			10	3.9	4	4.7
165 to 169	3	3.5	1	0.4	5	5.9
170 to 174	1	1.1	3	1.2	2	2.4
175 to 179			4	1.6	1	1.7
180 to 184	1	1.1	1	0.4		
185 to 189	1	1.1	3	1.2		
190 to 194					2	2.4
195 to 199					1	1.7
200 to 204						
205 to 209					1	1.7
210 to 214						
215 to 219					1	1.7
220 to 224						
225 to 229						
230 to 234			1	0.4		
235 to 239						
240 to 244					1	1.7
245 to 249						
Total	87	20.2	256	60.0	85	19.8
Mean		125.7		133.1		146.3
S. D.		18.8		18.9		23.0
P. F. of mean		1.4		0.8		1.7

in whom the figures are 122.1 ± 0.8 , 125.8 ± 0.8 , 135.3 ± 1.2 , 154.4 ± 1.7 . Figure 1 shows how, in the twenties, the pressures of the women average 10 mm. lower than those of the men and after 50 they average 10 mm. higher than the men. The average for all ages put together is practically the same in both sexes, that is, 134.5 ± 0.7 for the women, and 134.7 ± 0.7 for the men.

² Alvarez W. C. Blood Pressures in 15,000 University Freshmen, Arch Int Med 32:17 (July 15) 1923.

Table 2 shows that the pressures of those with a normal build and weight average some 8 mm higher than do those for the thin, and the pressures of the fat average 13 mm higher than do those of the normal

All the pressures were taken with the auscultatory method, with a mercury manometer and a standard cuff. The patients were reclining. If the pressure varied much, we used the mode of several readings made on the same or subsequent days.

TABLE 3—*Women, All Ages*

Blood Pressure	Normal Bowels		Chronic Constipation		Occasional and Recent Constipation		Diarrhea	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
From 90 to 94								
95 to 99	2	0.8	2	0.8	1	1.8		
100 to 104	4	1.5	6	2.4	2	3.6		
105 to 109	7	2.6	8	3.2	2	3.6		
110 to 114	17	6.4	21	8.5	4	7.3	3	17.6
115 to 119	25	9.5	27	10.9	7	12.7		
120 to 124	26	9.9	25	10.1	3	5.5	7	41.1
125 to 129	24	9.1	31	12.5	6	10.8		
130 to 134	32	12.1	28	11.3	4	7.3	1	5.9
135 to 139	22	8.3	17	6.8	3	5.5		
140 to 144	23	8.7	18	7.3	7	12.7	5	29.5
145 to 149	15	5.7	7	2.8	1	1.8		
150 to 154	11	4.2	15	6.0	2	3.6	1	5.9
155 to 159	11	4.2	9	3.6	3	5.5		
160 to 164	6	2.3	1	0.4	4	7.3		
165 to 169	4	1.5	6	2.4	2	3.6		
170 to 174	5	1.9	5	2.1				
175 to 179	7	2.6	6	2.4	1	1.8		
180 to 184	5	1.9	6	2.4				
185 to 189	3	1.1	1	0.4	1	1.8		
190 to 194	1	0.4	3	1.2	1	1.8		
195 to 199	1	0.4			1	1.8		
200 to 204	2	0.8	1	0.4				
205 to 209	3	1.1	1	0.4				
210 to 214	1	0.4	2	0.8				
215 to 219	1	0.4	1	0.4				
220 to 224	3	1.1						
225 to 229	1	0.4						
230 to 234			2	0.8				
235 to 239								
240 to 244								
245 to 249								
250+	2	0.8						
Total	264		249		55		17	
Mean	140.0		136.0		136.4		131.0	
Mean corrected	141.4		137.1		135.3		133.5	
S. D.	27.2		24.5		23.1		12.3	
P. E. of mean	1.1		1.0		2.1		2.0	
Corrections for age and weight								
Normal bowels				$140.0 \pm 1.1 \times 1.009 \times 1.0007 = 141.4 \pm 1.1$				
Chronic constipation				$136.0 \pm 1.0 \times 1.004 \times 1.004 = 137.1 \pm 1.0$				
Occasional and recent constipation				$136.4 \pm 2.1 \times 1.000 \times 0.992 = 135.3 \pm 2.1$				
Diarrhea				$131.0 \pm 2.0 \times 1.015 \times 1.004 = 133.5 \pm 2.0$				

BLOOD PRESSURE IN NORMAL, CONSTIPATED AND DIARRHEIC PERSONS

Tables 3 and 4 show the distribution of the data from the subjects in the four groups of normal, constipated, occasionally or recently constipated, and occasionally or recently diarrheic. These patients were all ambulant, all white, and for the most part from the middle and upper walks of life. Most of them came seeking relief from gastro-intestinal troubles.

The letters S D represent the standard deviation which is a measure of the scattering of the figures in the distribution. The P E, or probable error, of the mean is a most useful figure as it gives us an idea of the reliability of our averages. When, as in the case of the diarrheic patients, the group is small, we know we cannot argue very far on the basis of the means that we get. The figures 136.0 ± 3.2 mean that if we were to study another 10,000 cases, the odds are even that the average we would then obtain would lie somewhere between 139.2 and 132.8. In figure 2 we have shown the extent of the minus P E by cutting a nick out of the end of each column.

The value of this P E will be seen again when we come to appraise the significance of a difference between two means. The P E of a difference is the square root of the sum of the squares of the P E's of

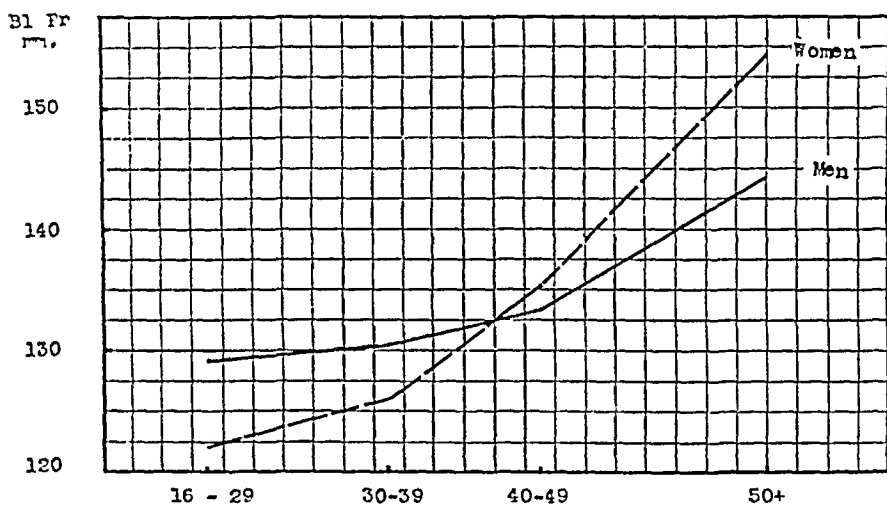


Chart 1—Mean blood pressure in men and women at different ages

the two measures being compared. If the difference is little larger than its probable error, we naturally can put little confidence in it. If it is 4 or 5 times as large as its P E, it is almost certainly significant.

On turning then, to figure 2, we see that among the men there is no significant difference between the pressures in the normal, the constipated, and the diarrheic. Among the women, strange to say, those with constipation average 4.3 mm. lower than the normal. This difference is 2.9 times its P E, which means that the odds are 18.8 to 1 that there is some significance behind it. It would be a hard blow to the apostles of auto-intoxication if it should turn out that a certain amount of constipation is good for a woman. The puzzling feature is that those with occasional or recent constipation have an even lower average pressure. We note, however, that there were only fifty-five in that group and the P E is 2.1 mm., so that, with a larger number of cases, the difference might be wiped out.

Some of the believers in intestinal poisoning may now assert that the blood pressure has been lowered in the constipated group by histamine-like toxins, but that will not explain why it did not happen in the men. Another difficulty in interpretation arises from the fact that one might just as well argue that hypertension has, perhaps, a slightly laxative effect on women. Some studies which we hope to publish soon show

TABLE 4—Men, All Ages

Blood Pressure	Normal Bowels		Chronic Constipation		Occasional and Recent Constipation		Diarrhea	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
From 90 to 94	1	0.6	1	0.6	1	1.8		
95 to 99	4	2.3	1	0.6				
100 to 104	2	1.2	3	1.8	1	1.8		
105 to 109	7	4.1	6	3.6	2	3.6		
110 to 114	6	3.5	13	7.9	5	9.1	4	22.2
115 to 119	14	8.1	16	9.7	2	3.6		
120 to 124	20	11.6	18	10.9	9	16.3	5	27.8
125 to 129	20	11.6	13	7.9	7	12.7		
130 to 134	24	14.0	18	10.9	10	18.2	3	16.6
135 to 139	16	9.3	9	5.5	5	9.1		
140 to 144	16	9.3	18	10.9	4	7.3	2	11.1
145 to 149	10	5.8	10	6.0	4	7.3		
150 to 154	11	6.4	10	6.0	1	1.8	1	5.6
155 to 159	5	2.9	3	1.8	2	3.6		
160 to 164	7	4.1	9	5.5	1	1.8	1	5.6
165 to 169	4	2.3	5	3.1				
170 to 174	1	0.6	4	2.4			1	5.6
175 to 179	1	0.6	1	0.6				
180 to 184			2	1.2			1	5.6
185 to 189	1	0.6	1	0.6	1	1.8		
190 to 194	1	0.6	1	0.6				
195 to 199			1	0.6				
200 to 204								
205 to 209			1	0.6				
210 to 214								
215 to 219	1	0.6						
220 to 224								
225 to 229								
230 to 234			1	0.6				
235 to 239								
240 to 244								
245 to 149								
Total	172		165		55		18	
Mean	133.9		136.2		130.2		136.2	
Mean corrected	134.0		136.0		134.5		136.1	
S. D.	18.8		22.3		15.1		20.3	
P. E. of mean	1.0		1.2		1.4		3.2	

Corrections for age and weight

Normal bowels

Chronic constipation

Occasional and recent constipation

Diarrhea

$$133.9 \pm 1.0 \times 1.007 \times 0.994 = 134.0 \pm 1.0$$

$$136.2 \pm 1.2 \times 0.995 \times 1.004 = 136.0 \pm 1.2$$

$$130.2 \pm 1.4 \times 1.008 \times 1.025 = 134.5 \pm 1.4$$

$$136.2 \pm 3.2 \times 0.996 \times 1.004 = 136.1 \pm 3.2$$

that this is not at all improbable, and that there are certain conditions which, while not laxative enough to produce diarrhea, are laxative enough to insure a high percentage of individuals with normal bowel movements. The low pressures found in women with diarrhea might easily be due to a slight debilitating effect from that condition. Against that interpretation is the fact that there is no lowering of the pressures in the diarrheic men. Unfortunately, the diarrheic groups are so small

TABLE 5—Age Distribution

Age Groups	Normal Bowels						Occasional and Recent Constipation						Diarrhea					
	Women			Men			Women			Men			Women			Men		
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent
16 to 29	75	28.4 ± 1.9	32	18.6 ± 2.0	52	20.9 ± 1.8	14	8.5 ± 1.5	11	20.0 ± 3.6	15	27.3 ± 3.7	5	29.4 ± 5.0	3	16.6 ± 5.9		
30 to 39	76	28.8 ± 1.9	53	30.8 ± 2.4	84	33.8 ± 2.0	53	32.0 ± 2.5	19	34.5 ± 4.3	19	31.5 ± 4.3	6	35.2 ± 7.8	7	38.9 ± 7.8		
40 to 49	51	19.3 ± 1.6	54	31.4 ± 2.4	53	21.2 ± 1.8	48	29.0 ± 2.4	10	18.2 ± 3.5	9	16.4 ± 3.5	2	11.8 ± 5.3	2	11.1 ± 5.0		
50+	62	23.5 ± 1.8	33	19.2 ± 2.0	60	24.1 ± 1.8	50	30.5 ± 2.4	15	27.3 ± 3.7	12	21.8 ± 3.6	4	23.5 ± 6.9	6	33.4 ± 7.5		
Total	264		172		249		165		55		55		17		18			

Weight Distribution

Body Build	Normal Bowels						Chronic Constipation						Occasional and Recent Constipation					
	Women			Men			Women			Men			Women			Men		
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent
Thin	62	23.5 ± 1.8	24	14.0 ± 1.8	63	25.2 ± 1.9	31	18.7 ± 2.0	11	20.0 ± 3.6	16	29.0 ± 4.0	4	23.5 ± 6.9	3	16.7 ± 5.9		
Normal	147	55.7 ± 2.1	105	61.0 ± 2.5	140	56.2 ± 2.1	104	63.0 ± 2.5	29	52.7 ± 4.5	37	67.0 ± 4.3	10	53.9 ± 8.1	12	66.6 ± 7.5		
Stout	55	20.8 ± 1.7	43	25.0 ± 2.2	46	18.6 ± 1.7	30	18.3 ± 2.0	15	27.3 ± 3.7	2	4.0 ± 1.7	3	17.6 ± 6.2	3	16.7 ± 5.9		
Total	264		172		249		165		55		55		17		18			

connection between constipation and a slightly lower mean blood pressure. It is possible that diarrhea is also associated with a lower pressure but our data are too few for a trustworthy conclusion.

It must be remembered in studying these data that there are three possible interpretations. The constipation may lower the pressure, lower pressures may cause the constipation, and higher pressure may be slightly laxative.

Standards are given for the correction of averages according to differences in age and weight distribution. It is seen that in men the blood pressure does not rise appreciably until after the age of 50. Blood pressure in women behaves differently.

Men with normal weight average 10 mm. higher than do the lean, and the stout average 13 mm. higher than the normal.

DISEASES OF THE LIVER

V A COMPARATIVE STUDY OF TESTS FOR HEPATIC FUNCTION IN CERTAIN DISEASES OF THE HEMATOPOIETIC SYSTEM [†]

CARL H GREENE, M D
AND
H MILTON CONNER, M D
ROCHESTER, MINN

The recent experiments of Mann, Bollman and Magath ¹ have shown that a dog will become jaundiced after the complete extirpation of the liver and that the injection of hemoglobin increases the rapidity with which the icterus develops. These observations indicate that the liver must be considered, at least to some extent, as an excretory organ for the bile pigments. The physiologic possibility of a true hemolytic jaundice of extrahepatic origin, a point that heretofore has not met with universal acceptance, must be recognized. The observations of van den Bergh,² Lepehne,³ McNee,⁴ Feigl and Querner⁵ and others on the changes in the van den Bergh reaction in cases of hemolytic jaundice have further served to emphasize the importance of a more accurate knowledge of the activity of the liver.

Jaundice may be produced by three separate pathologic processes (1) by a mechanical obstruction to the extrahepatic biliary passages with resultant resorption of bile pigments (so-called obstructive jaundice), (2) by the inability of the parenchymal cells of the liver to excrete the bile pigments in the normal manner (so-called hepatic jaundice), and (3) by destruction of erythrocytes and the formation of bilirubin more rapidly than normally, with consequent retention in the blood stream (so-called hemolytic or hematogenous jaundice).

We have previously reported a comparative study of certain tests of hepatic function in the different varieties of obstructive jaundice. We now report the results of a similar study in a carefully selected series

[†] From the Section on Medicine, Mayo Clinic

1 Mann, F C, Bollman, J L, and Magath, T B. Studies on the Physiology of the Liver. IX, The Formation of Bile Pigment After Total Removal of the Liver, *Am J Physiol* **69** 393-409 (July) 1924

2 Van den Bergh, A A H. Der Gallenfarbstoff im Blute, Leiden, S C van Doesburgh **8**, 1918

3 Lepehne, Georg. Untersuchungen über Gallenfarbstoff im Blutserum des Menschen, *Deutsches Arch f klin Med* **132** 96-120 (April) 1920, **135** 79-107 (Jan) 1921

4 McNee, J W. Jaundice. A Review of Recent Work, *Quart J Med* **16** 390-420 (July) 1923

5 Feigl, J, and Querner, E. Bilirubinämie in ihren physiologisch-chemischen Beziehungen mit besonderer Berücksichtigung der diagnostischen Bedeutung, *Ztschr f d ges exper Med* **9** 153-250, 1919

of cases of hemolytic jaundice and certain other diseases of the hemopoietic system. The theoretic basis of the different tests and the details of the technic used are given in the initial paper of this series.⁶ In order more fully to correlate the functional studies with the clinical picture it seems desirable to include a short summary of the principal clinical features of the different conditions studied. Abstracts of the histories of typical cases are given in more detail. Only significant laboratory data are included in these abstracts but the complete findings are given in the accompanying tables. The phenoltetrachlorophthalein test is reported in terms of the hour reading.

HEMOLYTIC JAUNDICE

The "hematogenous" jaundice of the older writers was originally descriptive of those cases in which icterus was present without manifest obstruction in the bile passages. The acceptance and use of this term has varied widely with the various theories regarding the rôle of the liver in the formation of bile pigment. The experiments of Whipple and Hooper⁷ and the recent studies of Mann, Bollman and Magath on dehepatized animals, showing the extrahepatic formation of bilirubin, afford the basis for the recognition of hemolytic jaundice as a distinct clinical and physiologic entity.

The characteristic features of this condition have recently been discussed by Tileston⁸ and Meulengracht.⁹ These include long continued icterus of moderate intensity without the pruritus or bradycardia characteristic of obstructive jaundice. The urine contains urobilin but no bile, while the stools are highly colored. The spleen is enlarged. Moderate anemia may be present. A marked feature is the presence of gallstone attacks, which are often assumed to be the cause of the icterus and may lead to operation,¹⁰ gallstones were present in 58 per cent of the cases at the Mayo Clinic in which splenectomy was performed. Most characteristic are the diminished resistance of the erythrocytes to hemolysis by hypotonic solution of sodium chloride and the presence of large numbers of reticulated red cells. We have not attempted the discussion separately of the congenital, or Minkowski-Chauffard, and the acquired, or Hayem-

6 Greene, C. H., Snell, A. M., and Walters, Waltman. Diseases of the Liver. I, A Survey of Tests for Hepatic Function, *Arch Int Med* **36** 248-272 (Aug.) 1925.

7 Whipple, G. H., and Hooper, C. W. Icterus. A Rapid Change of Hemoglobin to Bile Pigment in the Circulation Outside the Liver, *J Exper Med* **17** 612-635, 1913. Whipple, G. H. The Origin and Significance of the Constituents of the Bile, *Physiol Rev* **2** 440-459 (July) 1922.

8 Tileston, W. Hemolytic Jaundice, *Medicine* **1** 355-388 (Aug.) 1922.

9 Meulengracht, E. Der chronische hereditäre hamolytische Ikterus (konstitutionelle Hypersplenie), Leipzig, W. Klinkhardt, 1922.

10 Giffin, H. Z. Hemolytic Jaundice. A Review of Seventeen Cases, *Surg Gynec Obst* **25** 152-161 (Aug.) 1917.

Widal, forms of the condition. The majority of the cases belonged to the former group. The results of the different functional tests are shown in table 1.

CASE 1 (case 7, table 1) —A young man, aged 21, was admitted to the clinic, March 10, 1924, because of icterus and a left abdominal mass. One brother had been jaundiced, had had an enlarged spleen since childhood, and died at the age of 18 from an acute illness accompanied by fever and jaundice. The patient had been lemon yellow since the age of 3. For three years previous to admission he had had irregular gastro-intestinal upsets with nausea, vomiting and slight jaundice, but no colic. In January, 1925, he had a more severe attack, with vomiting, diarrhea, fever and jaundice for several days. An enlarged spleen was discovered at that time.

He was slightly icteric in appearance. The liver could not be felt although the spleen was slightly enlarged. The urine contained urobilin but no bile. The blood showed a marked secondary type of anemia with an increase in the fragility of the red cells. The differential leukocyte count was normal, but 23 per cent of reticulated erythrocytes were present. The serum bilirubin was 3.3 mg. for each hundred cubic centimeters of blood. There was no retention of phenoltetrachlorophthalein.

At operation, March 27, an enlarged spleen was removed. Chronic cholecystitis with multiple cholelithiasis was discovered and the gallbladder was excised, April 9. The jaundice rapidly disappeared and the postoperative recovery was uneventful.

PERNICIOUS ANEMIA

The clinical picture is well known.¹¹ Increasing emphasis is placed on the evidence of augmented destruction of blood. The lemon color of the patient, the presence of urobilin and urobilinogen in the urine and pleochromia in the bile, as emphasized by Schneider,¹² and particularly by Giffin, Sanford and Szlapka,¹³ are evidence of increased destruction of the blood. The varying relationship between the deficient formation of red blood cells and their excessive destruction seems to determine the condition of the blood at any particular time. The frequency with which the liver and spleen are enlarged indicates the importance of further knowledge concerning functional changes. The laboratory findings in a series of typical cases are given in table 1.

CASE 2 (Case 8, table 1) —A man, aged 59, developed a case of pernicious anemia with hemolytic crisis following transfusion. He first came to the clinic, Dec. 18, 1920, because of weakness and anemia of two months' duration. He was pale yellow. The spleen was palpable. The erythrocytes numbered 1,880,000, the leukocytes 2,600, and the hemoglobin was 28 per cent. Gastric achlorhydria was present and duodenal drainage showed an increase in the pigments in the bile. A

11 Minot, G. R. Clinical Discussion of the Anemias, Oxford Medicine 2 611-635, 1920.

12 Schneider, J. P. The Splenic Pathology of Pernicious Anemia and Allied Conditions. A Duodenal Method of Estimating Hemolysis, Arch. Int. Med. 17 32-41 (Jan.) 1916, Further Quantitative Study of the Duodenal Blood-Derived Pigments, Arch. Int. Med. 19 156-162 (Jan.) 1917.

13 Giffin, H. Z., Sanford, A. H., and Szlapka, T. L. The Estimation of Urobilin and Urobilinogen in the Duodenal Contents, Am. J. M. Sc. 155 562-579 (April) 1918.

TABLE 1—Hemolytic Icterus

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm	Jaundice	Spleen 1 ml if Grd. 0 to 4	Urine			Blood Count			Tragility Test		Blood Nitrogen				Bile Pigments (Serum)		Tolerance Blood Sugar, Mg for Each 100 Ce			Phenol tetra chlorophthalein			Comment					
							Urobilin	Bile Pigments	Hemoglobin %	Erythrocytes, Millions	Leukocytes	Retculated Erythrocytes per Cent	Initial Hemolysis	Complete Hemolysis	Urea	Uric Acid	Creatinine	Amino Acid Nitrogen	Bile Index	Serum Bilirubin Mg per 100 Ce	Van den Bergh Direct Reaction	Normal	1 Hour	2 Hours	Change	15 Minutes		1 Hour	2 Hours	Dye in Urine, Mg		
1	5/23/23	12	♀	0	1	0	+	0	08	520	9,600	0.40	0.32	5	27	3.2	2.0	65	27	7.7	0+	77	0+	77	78	71	3	14	8	9	0.5	Mild case, no operation
2	5/11/24	35	♀	3	1	3	+	0	76	117	1,300	0.46	0.36	5	27	3.2	2.0	65	49	4.9	0+	49	0+	49	78	71	3	11	6	3	0.9	Splenectomy
3	1/13/25	22	♀	0	1	2	+	0	51	263	9,100	0.50	0.38	28	35	3.3	1.1		46	4.6	0+	46	0+	46	78	71	3	10	6	2.5	Splenectomy	
4	8/16/23	11	♀	0	2	1	+	0	47	220	12,600	0.50	0.38	28	35	3.3	1.1											12	4	1	0.0	Liver in good condition, splenectomy
5	7/10/25	21	♀	0	1	2		51	317	7,800		0.50	0.38	40	22			61	57	0	77	88	84	11	7	2	1	7	2	1		Splenectomy, multiple cholelithiasis
6	6/20/25	22	♀	0	1	0	+	76	194	5,200		0.42	0.32		27	4.1	1.5		46	0	82	92	84	10	5	2	0	5	2	0		Mild case, no operation
7	3/12/25	21	♀	0	1	1		48	284	10,100		0.50	0.31		23	3.9	1.0		33	0					2	1	0	2	1	0	0.1	Splenectomy, multiple cholelithiasis
8	3/18/24	63	♂	1	1	1		14	088	1,000				115	121	10.6	3.0	7.1	87	26.2	+							24	24	22		Hemolytic crisis with jaundice following transfusion
9	3/19/24	53	♂	1	0	1	+	30	176	1,500									14	5.0	0+	100	117	108	17	7	8	2	8	2	0.5	Pernicious anemia
10	3/10/25	57	♂	1	0	0	+	44	237	5,000				35	34	1.2	1.1		6	1.6	0	100	100	108	17	7	10	3	0	0.6		
11	4/20/24	57	♂	0	0	0	+	70	376	6,000				31	34	4.1	1.5	5.9	6	3.3	0	100	100	108	17	7	10	3	0	0.6		
12	1/17/24	45	♂	0	0	0	+	42	190	6,100				27	38	4.1	1.5	5.9	8	3.3	0	100	100	108	17	7	10	3	0	0.6		
13	3/22/24	44	♂	0	0	0	+	54	227	6,100				36	33	3.5	1.8	6.2	8	3.0	0	83	103	89	20	6	3	2	0	0.3		
14	1/27/25	65	♂	15	0	0	+	25	104	5,800				34	34				2.4	0		91	110	96	19	5	1	0	0	0.0		
15	3/11/24	44	♂	0	0	0	+	52	211	5,000				34	24			6.1	5	2.2	0	91	110	96	19	5	1	0	0	0.0		
16	1/8/24	70	♂	0	0	0	+	40	181	7,000				34	24				6	1.5	0	103	110	105	7	4	4	1	0	0.5		
17	2/11/24	10	♂	0	0	0	+	47	221	2,700				27	27				2.0	0		90	110	86	20	4	4	1	0	0.3		
18	2/16/25	39	♂	0	0	1		25	132	3,200				27	27				2.6	0		90	110	86	20	4	4	1	0	0.0		
19	2/20/24	53	♂	0	0	0	+	58	223	5,200				27	29				5	1.4	0					3	3	0	0	0.0		

* In this and the following tables, ♂ indicates male, ♀ female, †, just palpable, ‡, markedly enlarged, † + indicates a "prompt" direct reaction, ‡ + indicates a "delayed" direct reaction, and 0, in indirect reaction

diagnosis of pernicious anemia was made at that time. In the succeeding three and one-half years he was under close observation, the disease following a typical course with frequent remissions. He received a total of forty-eight transfusions during this period.

He returned, March 10, 1924 (the eleventh time). Ten days before he had suddenly become much weaker, and the anemia more marked. He was lemon yellow. The spleen was palpable but the liver could not be felt. A small amount of free fluid was present in the abdomen. The erythrocytes numbered 870,000, the leukocytes 3,900, and the hemoglobin was 18 per cent. He was given three transfusions of 250 cc each during the succeeding week.

Following the second transfusion, jaundice developed and increased rapidly in intensity. March 18, two days after the last transfusion, the erythrocytes numbered 880,000, the leukocytes 1,600, and the hemoglobin was 14 per cent. The jaundice was marked. The liver was enlarged and the edge could be felt 4 cm below the costal margin. The serum bilirubin was 26.2 mg for each hundred cubic centimeters of blood. There was retention of phenoltetrachlorophthalein, with a reading of 24 per cent. The urine contained albumin and bile, but no casts. The urinary output varied between 700 and 1,200 cc daily at this time. The blood urea was 122 mg. Improvement followed the initial hemolytic crisis. The jaundice disappeared and the blood urea fell to 52 mg by April 5. This improvement was only temporary and the patient died a week later with evidence of myocardial failure. Necropsy was not permitted.

The similarity is striking between the changes associated with the hemolytic crisis in this patient and the artificial hemolytic crisis produced by the therapeutic use of phenylhydrazine.

CASE 3 (case 12, table 2)—A man, aged 45, was admitted to the clinic, April 15, 1924, because of weakness and loss of strength during the preceding year. Ten years before, he had had a sore tongue, and gastric achlorhydria was discovered at that time. The sore tongue recurred irregularly but he was not too ill to work. In 1923, he began to lose weight, pallor was pronounced and he became very weak, with dyspnea and palpitation on slight exertion.

He was pale and slightly lemon colored. There was a moderate degree of glossitis. The liver could not be felt but the spleen was palpable. The urine contained a trace of albumin and urobilin. The erythrocytes numbered 1,900,000, the leukocytes 6,100, and the hemoglobin was 42 per cent. Gastric achlorhydria was present. The serum bilirubin was 3.3 mg. There was no retention of phenoltetrachlorophthalein. He was given three transfusions, with temporary improvement, but died ten months later.

SPLENIC ANEMIA (BANTI'S DISEASE)

Splenic anemia is of particular interest because of the frequent association of hepatic cirrhosis in the later stages of the disease. On the other hand, moderate enlargement of the spleen is an almost constant accompaniment of atrophic cirrhosis of the liver. In this study we have applied the term splenic anemia to a group of cases in which the characteristic features are the progressive enlargement of the spleen without known cause, the occurrence of gastric or intestinal hemorrhages, and the presence of an anemia, of varying degree, of the so-called secondary type, associated with leukopenia and often with relative lymphocytosis.¹⁴

¹⁴ Osler, William. On Splenic Anemia, *Am J M Sc* **119** 54-73, 1900, *Anemia Splenica*, *Tr A Am Phys* **17** 429-461, 1902.

TABLE 2—*Splenic Anemia*

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm	Jaundice	Weight of Spleen, Gm	Blood Count				Blood Nitrogen Partition, Mg for Each 100 Cc				Bile Pigments (Serum)		Fructose Tolerance Blood Sugar, Mg for Each 100 Cc				Phenoltetra chlorophthalein Dye in Serum, per Cent				Comment						
							Hemoglobin, %	Erythrocytes, Millions	Leukocytes	Phenolsulphonphthalein per Cent	Urea Nitrogen	Urea	Uric Acid	Creatinine	Amino Acid Nitrogen	Bile Index	Serum Bilirubin Mg per 100 Cc	Van den Bergh	Normal	1 Hour	2 Hours	5 Change	15 Minutes	1 Hour		2 Hours	Dye in Urine, Mg				
20	5/21/21	32	♀	1	0	550	+	Asclites	Urobilin	45	3.36	2,900	75	28	12	3.1	1.1	7.0	15	3.4	+	83	108	96	5	23	17	12	1.3	Cirrhosis observed at operation	
21	9/10/23	55	♂	3	1	8	0	+	+	60	3.25	3,200	75	11	2.9	1.3					+	16	14	7	0.0					Cirrhosis	
22	3/27/21	60	♀	8	1	810	0	+	+	68	3.91	3,800	55	28	23	3.5	1.8	7.1	15	2.5	0		13	10	6	0.1					Cirrhosis observed at operation
23	6/11/21	15	♀	0	0	630	0	0	0	65	3.89	6,000		36	28	2.9	1.6	6.6	10	1.1	+	90	120	87	30	11	8	1	0.3	Perihepatitis observed at necropsy	
24	3/20/21	51	♀	6	1	730	0	0	0	11	3.73	6,000	40	39		1.5	1.5	5.6	13	1.3	0	100	145	121	45	10	8	5	0.0	Cirrhosis observed at necropsy	
25	1/7/21	52	♀	0	0	8	0	0	0	39	2.71	3,700		27	12	3.9	1.2	7.4		2.5	0	104	135	108	30		8	4	0.0	Cirrhosis observed at operation	
26	11/8/21	10	♂	0	0	630	0	0	0	70	1.06	5,000		28	11	3.0	1.2	5.0	15	2.3	+		10	7	5	0.5					Cirrhosis observed at necropsy
27	10/17/21		♂	0	0	550	0	0	0	33	2.95	3,600		31	24	3.9	1.5	6.8	8	1.0	0		8	7	1	0.3					Cirrhosis observed at necropsy
28	3/21/21	53	♀	0	0	8	++	+	+	73	1.90	2,200		44		3.1	1.6	7.0	8		127		9	6	1						Cirrhosis, 19 months after splenectomy
29	10/11/21		♂	0	0	1,800	++	+	+	63	1.36	2,100	80	34	19		1.2	6.7		0.5	0		9	6	3						
30	12/21/21	37	♂	0	0	1,800	0	+	+	72	4.34	7,600		47	14					1.2	0										
31	3/27/21	19	♀	8	0	800	++	+	+	10	1.26	3,000	70	31	27	3.0	1.6	7.2	12	1.9	0	105	143	121	38		5	3	0.6		
32	7/3/23	11	♀	+	0	890	0	0	0	58	1.06	3,300		37	31	3.0	1.2			0.3	0		8	5	0						12 months after sple
33	3/5/25	34	♀	8	0	1,000	0	0	0	70	4.51	10,700		36	30						0		8	4	2						necromy
34	1/22/21	32	♀	0	0	800	+	+	+	35	2.92	3,000	50	24	17	2.8	1.0			0.9	0		8	3	0						12 months after sple
35	2/9/25	27	♀	8	0	920	0	0	0	77	1.89	7,600		20	20					0.3	0		7	3	0						necromy
36	4/30/25	53	♂	1	8	1,050	++	1	+	46	2.26	7,400		19					8	2.1	0		5	2	0						Cirrhosis observed at operation
37	2/20/21	36	♀	+	0	1,050	+	+	+	31	3.06	3,300		33	20					0.7	0		5	2	0						Cirrhosis observed at operation
38	1/5/21	27	♂	8	0	900	0	0	0	32	2.17	5,100	50	25	20	2.0	2.0	5.3	1.0	0	104	117	103	13		2	0	0.3			
39	12/2/24	16	♀	8	0	1,800	0	0	0	68	1.03	4,300		26	21	2.9	1.1	6.2		0.7	0	130									
40	6/18/25	50	♂	0	0	8	++	+	+	51	3.26	7,000		30	26	1.5				1.1	0	76	96	100	21		5	2	0	0.7	Splenomegaly—Gaucher Type

Clinical evidences of hepatic disturbance are less marked. Cirrhosis, ascites and occasionally jaundice may appear in the later stages of the disease. The results of the different functional tests are shown in table 2.

CASE 4 (case 33, table 2) —A man, aged 32, had his first hematemesis in June, 1917, vomiting blood clots and fresh blood repeatedly for twelve hours. He was subsequently pale and weak, the stools were tarry, and he was in the hospital for a week. Recovery was gradual. Since then he had had five or six similar attacks, which usually followed severe exertion. Ascites followed the last hemorrhage six weeks before admission, Jan. 22, 1924.

He was pale and weak with a waxy white skin. Ascites was marked and the superficial abdominal veins were distended. After paracentesis an enlarged spleen could be felt but the liver was not palpable. The urine was normal. Blood counts showed a marked secondary type of anemia with leukopenia. The serum bilirubin was 0.9 mg. There was no retention of phenoltetrachlorophthalein.

At operation, February 27, an enlarged spleen weighing 800 Gm. was removed with great difficulty. The liver was apparently in good condition. Following the operation the ascites disappeared and recovery was uneventful.

CASE 5 (case 22, table 2) —A man, aged 60, had an attack of hematemesis in November, 1923. At that time he fainted, then vomited clots and fresh blood. The stools were tarry for several days afterward. A second attack in February, 1924, followed severe exertion.

He was subicteric in appearance when examined, March 27, 1924. He was quite obese but ascites was demonstrable. The edge of the liver extended 8 cm. below the costal margin, and the spleen was markedly enlarged. The urine contained urobilin but no bile. Moderate secondary anemia with leukopenia was present. The serum bilirubin was 2.5 mg. There was retention of phenoltetrachlorophthalein with a reading of 10 per cent.

At operation, April 15, a large spleen weighing 810 Gm. was removed. The liver was enlarged and cirrhotic in appearance. Postoperative recovery was slow and the ascites persisted for a long time. The patient was able to resume his normal activities but died, Jan. 16, 1925, following another gastric hemorrhage.

SPLENOMEGALY OF THE GAUCHER TYPE

Splenomegaly of the Gaucher type is of particular interest because it is considered as an example of primary overgrowth of the cells of the reticulo-endothelial system.¹⁵ Mandelbaum¹⁶ has reviewed the pathologic changes in detail and points out that infiltration of the liver is not uncommon. We are able to report studies on one case (table 2). Histologic examination of the spleen was not possible but the clinical features were rather characteristic and distinct.

CASE 6 (case 39, table 2) —A man, aged 50, was admitted to the clinic, June 18, 1925, because of splenomegaly of fourteen years' duration. In 1910 he first noted a mass in the left side which slowly increased in size. His physician made a diagnosis of splenomegaly in 1917. Since that time there had been a progressive painless enlargement of the spleen. Anemia developed slowly during this period.

15 Waugh, T. R., and MacIntosh, D. S. The Histogenesis and Nature of Gaucher's Disease, *Arch. Int. Med.* **33**: 599-610 (May) 1924.

16 Mandelbaum, F. S. Two Cases of Gaucher's Disease in Adults. A Study of the Histopathology, Biology and Chemical Findings, *Am. J. M. Sc.* **157**: 366-389 (March) 1919.

TABLE 3—*Polycythemia Vera*

Case	Date	Age, Years	Sex	Edge of Liver Palpable, Cm	Spleen Enlarged	Urine		Blood Count			Whole Blood Volume Cc for Each Kg	Phenolsulphonphthalein, per Cent	Blood Nitrogen Partition, Mg for Each 100 Cc				Bile Pigments (Serum)		Fructose Tolerance Blood Sugar, Mg for Each 100 Cc			Phenoltetra-chlorophthalein			Comment						
						Specific Gravity	Albumin	Trobin	Hemoglobin, %	Erythrocytes, Millions			Leucocytes	Urea	Uric Acid	Creatinine	Amino Acid	Serum Bilirubin, Mg per 100 Cc	Van den Bergh Direct Reaction	Normal	1 Hour	2 Hours	Change	15 Minutes		1 Hour	2 Hours	Dye in Serum, per Cent	Dye in Urine, Mg		
40	0/16/25	46	M	0	0	1.020	0	0	141	689	9,500	107	40	15	11	34	14	11	0	1.5	0	105	81	109	87	25	12	5	0	0.6	Before treatment During treatment with phenylhydrazine
41	7/15/25	59	M	0	0	1.026	0	0	170	711	8,700	165	40	53	47	49	14	11	3	1.0	0	107	122	108	15	15	8	5	0	0.6	Before treatment During treatment with phenylhydrazine
42	4/17/25	59	M	0	0	1.018	1	2	214	836	6,700	190	55	19	45	29	18	89	0.9	0	75	98	92	23	16	8	3	0	0	Before treatment During treatment with phenylhydrazine	
43	5/1/25	62	M	0	0	1.015	1	+	150	497	15,000	136	35	62	52	40	22	11	3	2.4	0	81	97	83	16	16	3	1	0	0	Before treatment During treatment
44	12/15/24	62	M	0	0	1.075	1	0	103	785	11,000	183	40	16	29	16	92	17	0	0	0	8	3	0	0	0	3	1	0	0	Before treatment During treatment
45	2/9/25	58	M	0	0	1.006	2	+	150	658	21,000	172	75	45	26	28	22	14	3	1.7	0	76	86	100	24	24	7	3	1	0.5	Gout
Myelogenous Leukemia																															
46	4/23/25	22	M	0	0	1.018	1	0	36	337	459,000	69	28	51	18	11	3	0.1	0	0	0	76	86	100	24	24	7	3	1	0.3	
47	4/20/25	22	M	0	0	1.023	1	0	40	311	360,000	75	26	29	15	21	2	0.1	0	0	0	86	95	89	9	9	6	2	0	0.3	
48	4/21/25	30	M	0	0	1.017	1	0	70	413	199,000	63	22	37	14	9	4	0.3	0	0	0	86	95	89	9	16	7	3	0	0	After radium treatment
49	5/5/25	57	M	0	0	1.027	0	0	46	335	83,000	37	29	37	10	7	3	0.1	0	0	0	114	98	111	16	16	7	3	0	0.5	After radium treatment
50	8/20/25	15	M	0	0	1.026	0	0	47	350	51,000	30	31	28	7	1	0.1	0	0	0	0	0	0	0	0	6	2	0	0	0	After radium treatment
Lymphatic Leukemia																															
51	0/12/25	53	M	0	0	1.010	1	0	22	221	227,400	42	24	30	19	7	9	0.1	0	0	0	100	106	111	11	11	7	5	2	0	
52	7/12/25	37	M	0	0	1.020	0	0	56	399	116,000	59	12	45	60	0.4	0	0	0	0	0	82	100	94	18	18	7	3	0	0	
53	6/10/25	53	M	0	0	1.030	0	0	59	406	75,000	33	33	35	13	69	0.4	0	0	0	0	111	142	118	31	31	7	3	1	0	
54	6/5/25	61	M	0	0	1.019	0	0	70	451	6,800	34	33	22	20	7	3	0.4	0	0	0	81	93	83	12	12	2	1	0	0	After radium treatment

Myelogenous Leukemia

Lymphatic Leukemia

but apart from that and the fulness of the abdomen, he felt well, and he was able to continue his usual work. One sister was reported to have had a large spleen.

The patient appeared moderately anemic, with characteristic pigmentation of the face and neck and pinguecula of the cornea. The spleen was very large, practically filling the abdomen. Moderate anemia of secondary type was present. The erythrocytes numbered 3,260,000, the leukocytes 7,000, and the hemoglobin was 54 per cent. The differential leukocyte count was normal. The serum bilirubin was 1.1 mg, and there was no retention of phenoltetrachlorophthalein.

POLYCYTHEMIA VERA (ERYTHREMIA)

True polycythemia is the converse of anemia in that it is characterized by a persistent increase in the red blood corpuscles with resultant plethora. The clinical features of the condition have recently been discussed by Fitz¹⁷ Brown and Giffin¹⁸ have followed the changes in the total blood volume and particularly stress the vascular readjustments to the increased volume of the circulating blood. We are able to report additional studies on some of these cases. These are of particular interest in that phenylhydrazine was used therapeutically in four. We are able, therefore, to compare the changes in true hemolytic icterus with those in the artificial hemolytic icterus produced by this means.

CASE 7 (case 40, table 3) — A woman, aged 31, came to the clinic, June 15, 1925, because of stomach trouble of six years' duration. It began with pain in the epigastrium and along the left costal margin, accompanied by nausea but not by vomiting. The attacks became more frequent and were associated with severe headaches which recurred every two weeks. In 1922, a tumor in the left side of the abdomen was discovered by the family physician. He removed the appendix and gallbladder but did not disturb the tumor. Since then the patient has been worse, with frequent attacks of headache, and pain in the left upper quadrant of the abdomen, accompanied by nausea and vomiting.

The patient was asthenic and weighed but 108 pounds (49 Kg), having lost 25 pounds (11.3 Kg) in about two years. The face and hands were a full dusky red, the lips bluish, and the nails cyanotic. Ophthalmoscopic examination showed the retinal veins to be full and congested. The heart was not enlarged and the sounds were clear. The spleen was enlarged and extended 3 cm below the costal margin. The liver was not palpable. There was a marked polycythemia, the erythrocytes numbering 6,890,000, while the blood volume was 176 cc for each kilogram of body weight. The blood urea was 11 mg. The serum bilirubin was 1.5 mg, and there was no retention of phenoltetrachlorophthalein.

The patient was then given phenylhydrazine by mouth in a dosage of 0.3 Gm daily for a period of twelve days. In all 3.5 Gm of the drug was given. During this period there was marked destruction of red blood cells. The cyanosis disappeared. The liver enlarged until the edge was palpable 3 cm below the costal margin. The spleen reached a level 6 cm below the costal margin. The erythrocyte count decreased to 4,200,000, and the whole blood volume to 104 cc for each kilogram of body weight. The serum bilirubin increased to 7.7 mg, and slight jaundice appeared (fig 1). Urobilin and urobilinogen appeared in the urine. The blood urea increased to 69 mg and albumin and red blood cells appeared in the urine. The phenolsulphonphthalein excretion, however, was 65 per cent at this time. There was no change in the excretion of phenoltetrachlorophthalein. The

17 Fitz, Reginald. Polycythemia, *Oxford Med* 2 763-778, 1920.

18 Brown, G. E., and Giffin, H. Z. Studies of the Vascular Changes in Cases of Polycythemia Vera, *Am J M Sc* 171 157-168, 1926.

administration of the phenylhydrazine was stopped. Thereafter, the jaundice rapidly disappeared and the liver and spleen returned to their original dimensions. The erythrocyte count fell to 2,500,000, and the blood volume to 89 cc for each kilogram of body weight, and then became stationary. The urine again became normal. The blood urea was 24 mg. The serum bilirubin returned to normal. The patient was dismissed, July 23, with complete symptomatic relief.

LEUKEMIA

The usual case of leukemia is characterized by a marked increase in the leukocytes of the blood associated with hyperplasia of the leukoblastic tissues. In cases of the myelogenous type the spleen may be very greatly enlarged, while the lymphatic form is not characterized by appreciable splenomegaly but by lymphglandular enlargement. Enlargement of the liver is common and is usually associated with infiltration by the leukemic elements from the blood. The effect of such changes on the functional efficiency of the liver is of extreme interest. The findings in a series of characteristic cases are shown in table 3.

CASE 8 (case 46, table 3) —A man, aged 28, was admitted to the clinic, April 21, 1925, because of increasing weakness over a period of three months. Loss of strength and energy had been marked. A mass under the left costal margin had been noted two months before admission. There was no gastro-intestinal disturbance.

The patient was pale and thin, weighing but 115 pounds (52.1 Kg). The superficial lymph nodes in the groin were enlarged. The liver extended 4 cm below the costal margin. Its surface was smooth and the edge rounded. The spleen was tremendously enlarged and filled the whole left side of the abdomen. Blood smears showed myelogenous leukemia with a leukocyte count of 459,000. Moderate anemia of secondary type was present. The serum bilirubin was 0.1 mg. There was no retention of phenoltetrachlorophthalein. Following the application of radium over the spleen the condition improved markedly.

CASE 9 (case 51, table 3) —A woman, aged 53, first noted a small nodule in the right submamillary region in 1924. This slowly increased in size at first, but in January, 1925, the growth became more rapid and other tumors appeared, first in the cervical, and then in the axillary and inguinal regions. Two months before admission, June 4, 1925, asthenia and weakness became marked.

There was a marked general enlargement of lymph nodes. The right cervical region in particular was occupied by a mass of large confluent nodules of varying consistency. There was a mass in the right axilla. The liver edge was just palpable but the spleen could not be felt. The erythrocytes numbered 2,210,000, and the hemoglobin was 22 per cent. The leukocytes numbered 227,400, and a differential count showed the presence of 98 per cent of lymphocytes. The serum bilirubin was 0.1 mg. There was no retention of phenoltetrachlorophthalein.

INDIVIDUAL TESTS

Fructose Tolerance —The fructose tolerance was studied in three cases of hemolytic jaundice with a normal response in all. No disturbance was noted in the five cases of pernicious anemia in which this test was made. This is in accord with the results of Kahn and Barsky,¹⁹

19 Kahn, Max and Barsky, Joseph. Studies of the Chemistry of Pernicious Anemia, Arch. Int. Med. 23: 334-345 (March) 1919.

who found the Bauer and Strauss tests negative in two cases of pernicious anemia. Similar results were secured by Hetényi.²⁰

Six cases of splenic anemia were studied. A positive fructose test was obtained in three and a suggestive test in one other. Goebel²¹ has reported positive fructose and galactose tests in two cases, and considers them evidence of hepatic cirrhosis. The extent of change in the fructose tolerance tests observed in our cases did not uniformly agree with the extent of the changes visible in the liver at the time of operation. In the cases of cirrhosis with ascites of the Laennec type positive fructose tolerance tests were irregularly obtained.²² In splenic anemia, then, we do not feel that a negative test can be used to exclude the presence of changes in the liver.

Negative tests were obtained in the cases of polycythemia. This was so even during the course of treatment with phenylhydrazine. Bodansky²³ has reported a marked decrease in the sugar tolerance of dogs as a result of toxic doses of phenylhydrazine. The dose, however, was such as to produce toxic lesions in the liver.

Tests were made in seven cases of leukemia. A reduction in the fructose tolerance was observed in one. A normal response was obtained in the case of Gaucher's splenomegaly.

There was no disturbance in the fasting blood sugar level in any of the cases studied. Mann and Magath²⁴ have emphasized the rôle of the liver in carbohydrate metabolism. They have likewise emphasized the relatively small proportion of the whole organ that is needed to maintain this activity. We have previously pointed out²⁵ that the most striking changes in sugar tolerance are those produced experimentally by poisons that cause direct toxic injury to the organ as a whole. Iron may be deposited in the liver in large amounts in cases of pernicious anemia or hemolytic icterus, and the liver may be enlarged as the result

20 Hetényi, Géza. Die Funktionsprüfung der Leber mittels gleichzeitiger Bilirubinbestimmungen im Blutserum und in der Galle, *Ztschr f klin Med* **95** 469-490 (Nov 30) 1922, abstr *J A M A* **80** 517 (Feb 17) 1923, Die Leberfunktion und ihre Bedeutung in der perniziösen Anämie, *Wien klin Wchnschr* **37** 1138-1140 (Oct 30) 1924.

21 Goebel, F. Banti'sche Krankheit und Leberfunktion zur Abgrenzung gegen die Leber cirrhose, *Deutsches Arch f klin Med* **146** 202-211 (Feb) 1925.

22 Greene, C H, McVicar, C S, and Rowntree, L G. Diseases of the Liver VI, The Functional Changes Accompanying Cirrhosis, to be published.

23 Bodansky, Meyer. The Action of Hydrazine and Some of Its Derivatives in Producing Liver Injury as Measured by the Effect on Levulose Tolerance, *J Biol Chem* **58** 799-811 (Jan) 1924.

24 Mann, F C, and Magath, T B. Studies on the Physiology of the Liver II, The Effect of the Removal of the Liver on the Blood Sugar Level, *Arch Int Med* **30** 73-84 (July) 1922.

25 Greene, C H, McVicar, C S, Rowntree, L G, and Walters, Waltman. Diseases of the Liver IV, Functional Tests in Carcinoma of the Liver and Biliary Tract, *Arch Int Med* **36** 542-560 (Oct) 1925.

of infiltration with fat in cases of pernicious anemia or by leukoblastic cells in cases of leukemia. These changes may be striking from the histologic point of view but the functional changes in the cases studied by us were apparently not comparable in magnitude. We have not been able to show clinically significant changes by means of the fructose tolerance test.

Nitrogen Partition of the Blood—Kahn and Barsky¹⁹ found no particular change in the nitrogen partition of the blood in cases of pernicious anemia. Gettler and Lindeman,²⁶ on the other hand, found the nonprotein nitrogen, urea, uric acid and creatinine to be slightly increased. This increase, which was not marked, they attributed to decreased volume of the blood. Keith,²⁷ however, has found that in

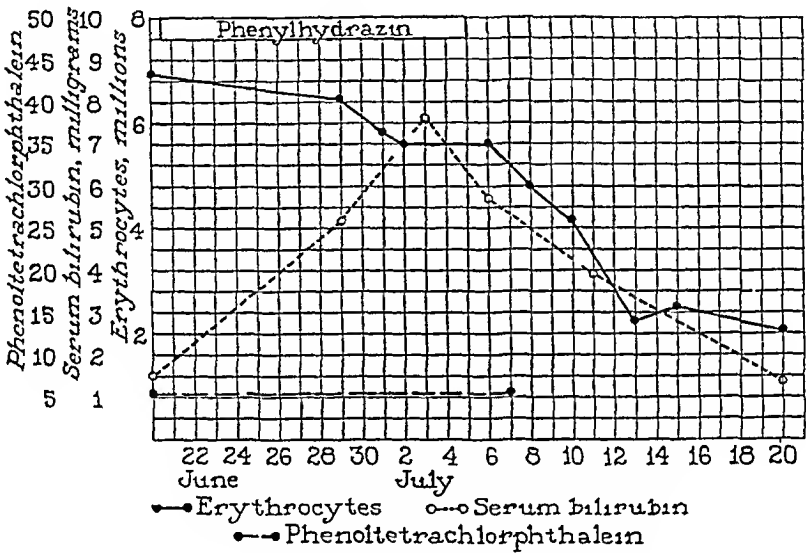


Fig 1—Changes in serum bilirubin, phenoltetrachlorophthalein and erythrocytes in case 7 during artificial hemolytic crisis produced by therapeutic use of phenylhydrazine

cases of pernicious anemia the whole blood volume is normal while the plasma volume may be markedly increased in consequence of the lowered erythrocyte content.

We found no characteristic changes from the normal in the non-protein nitrogenous constituents of the blood in cases of pernicious anemia, hemolytic jaundice or splenic anemia. The blood urea and total nonprotein nitrogen were increased following a hemolytic crisis in one patient with pernicious anemia (case 2). The urinary output of this patient was adequate and the blood urea returned toward normal as the jaundice disappeared. Similar changes were observed in the

26 Gettler, A. O., and Lindeman, E. Blood Chemistry of Pernicious Anemia, Arch Int Med 26 453-458 (Oct) 1920.
27 Keith, N. M. The Total Circulating Volume of Blood and Plasma in Cases of Chronic Anemia and Leukemia, Am J M Sc 165 174-184 (Feb) 1923.

cases of polycythemia vera during treatment with phenylhydrazine. The changes in both instances were apparently determined by an increased destruction of erythrocytes and a flooding of the organism with the products of protein catabolism. An analogy may well be drawn to the effect of a meat meal, or to the effect of a diet high in protein.

The most striking change found by Gettler and Lindeman in cases of pernicious anemia was a fourfold increase in the amino-acid nitrogen. The values for the amino-acid nitrogen in cases of pernicious anemia, hemolytic icterus and splenic anemia obtained by the Folin technic came within the normal limits suggested by Greene, Sandiford and Ross.²⁸ In cases of leukemia, on the other hand, as pointed out by Okada and Hayashi,²⁹ and by Sandiford, Boothby and Giffin,³⁰ there is a striking increase in the amino-acid nitrogen. This is particularly true in cases of myelogenous leukemia. We found similar changes in cases of polycythemia vera, although they were less striking than those found in cases of leukemia.

Martin, Denis and Aldrich³¹ found evidence of an increase in the rest nitrogen in the blood in cases of leukemia, and suggested that this increase might be due to amino-acids. We have found a similar increase in the rest nitrogen of the whole blood. This is most marked in cases of myelogenous leukemia and least in cases of polycythemia vera. The changes in leukemia correspond roughly to the increase in the leukocyte count. The amino-acids are increased under these conditions, but the increase is not sufficient to account for the whole of the changes in the rest nitrogen. The unknown substance apparently is a product of cellular activity since it is greater in the corpuscles than in the plasma or serum and is present in largest amounts in the leukocytes. Grafe³² especially has emphasized the metabolic activity of the white corpuscles in cases of leukemia. The increase in the rest nitrogen of the blood is perhaps additional evidence on this point.

Serum Bilinubin—The yellow color of the serum in cases of pernicious anemia was pointed out by Naegeli,³³ and has since been

28 Greene, C. H., Sandiford, Kathleen, and Ross, Helen. The Amino-Acid Content of the Blood in Normal and Pathologic Conditions, *J Biol Chem* **58** 845-857 (Jan) 1924.

29 Okada, S., and Hayashi, T. Studies on the Amino-Acid Nitrogen Content of the Blood, *J Biol Chem* **51** 121-133 (March) 1922.

30 Sandiford, Kathleen, Boothby, W. M., and Giffin, H. Z. The Amino-Acid Nitrogen in the Blood and Its Possible Relation to the Elevation of the Metabolism in Myelogenous Leukemia, *J Biol Chem* **55** 23-24, 1923.

31 Martin, C. I., Denis, W., and Aldrich, Martha. A Chemical Study of Blood Changes Following Roentgen-Ray Treatment of Leukemia, *Am J M Sc* **160** 223-233 (Aug) 1920.

32 Grafe, E. Die Steigerung des Stoffwechsels bei chronischer Leukämie und ihre Ursachen, *Deutsches Arch f klin Med* **102** 406-430, 1911.

33 Naegeli, Otto. *Blutkrankheiten und Blutdiagnostik*, Ed. 3, Berlin, W. de Gruyter and Co., 1919.

emphasized by Brockbank,³⁴ Riggs,³⁵ Gram³⁶ and others Blankenhorn,³⁷ by means of the Gmelin test, was able to demonstrate the presence of bilirubin in the serum. More exact studies dealing with determination of the precise quantities of bilirubin present have been made by van den Bergh,² Lepehne,³ and Broun, Ames, Warren and Peabody³⁸. The last mentioned, especially, have followed the changes in the plasma bilirubin over a period of time and report the close relationship between an increase in this pigment and the clinical exacerbations of the disease.

The cases of pernicious anemia studied in the present series show similar changes. In the majority the amount of serum bilirubin was at the upper limit of the normal, or slightly increased beyond these limits, the amounts varying from 1.4 to 5 mg. for each hundred cubic centimeters of blood (fig. 2). In none of these cases was a true "prompt"

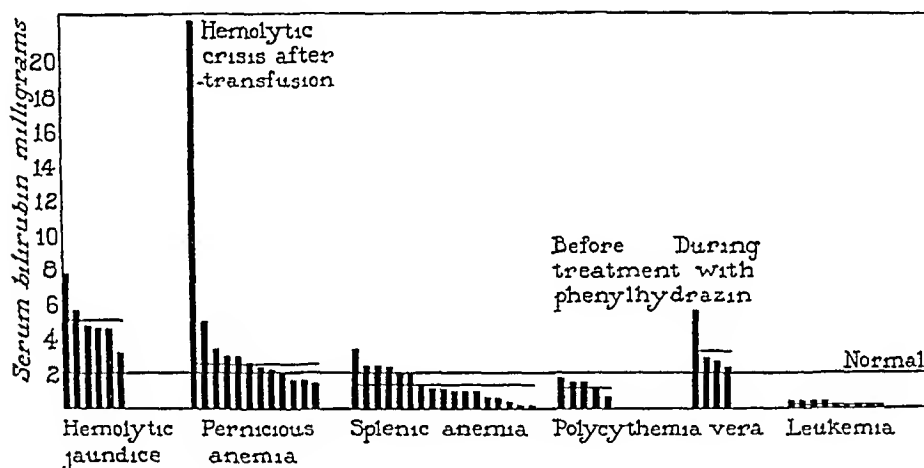


Fig. 2—Variation in serum bilirubin in different diseases of the hematopoietic system, the maximal normal level is indicated, and in each group the average value is shown by the horizontal line

direct van den Bergh reaction obtained. The reaction was either "indirect" or "delayed." Differences in the methods of interpreting the results of this test will explain the higher proportion of "delayed" reactions reported by Broun, Ames, Warren and Peabody³⁸. In one case (case 2) following a hemolytic crisis, frank jaundice developed. The

34 Brockbank, E. M. The Blood Serum in Pernicious Anemia, with Notes on the Nature of the Disease and Its Treatment, *Brit. M. J.* 2: 124-126 (July 22) 1922.

35 Riggs, C. E. Preliminary Note. A Study of the Nervous Syndrome and the Blood Serum in Pernicious Anemia as an Aid in Diagnosis Before Recognizable Changes Are Apparent. *Minnesota Med.* 7: 484-495 (July) 1924.

36 Gram, H. C. Meulengracht's Plasma Color Determination, *Ugeskr. f. Læger* 82: 1137-1139 (Sept. 2) 1920.

37 Blankenhorn, M. A. The Bile Content of the Blood in Pernicious Anemia, *Arch. Int. Med.* 19: 344-353 (March) 1917.

38 Broun, G. O., Ames, O., Warren, S., and Peabody, F. W. Blood Pigments in Pernicious Anemia, *J. Clin. Invest.* 1: 295-316, 1925.

serum bilirubin was increased to 262 mg for each hundred cubic centimeters of blood and a "prompt" direct van den Bergh reaction was obtained

The serum bilirubin was uniformly increased in the cases of hemolytic icterus, varying from 33 to 77 mg. The van den Bergh reaction was "indirect" in the majority of these cases although a "delayed" reaction was obtained in one and a "direct" reaction in case 1 (table 1), showing the most marked icterus. Biliary obstruction by associated gallstones may serve to explain the "direct" reaction in such cases.

In five of the cases of splenic anemia there was slight bilirubinemia, normal values were obtained in the others. There seemed to be no direct relation between the amount of serum bilirubin and the degree of the anemia in these patients.

Normal values for the serum bilirubin were obtained in five of the cases of polycythemia vera. Three of these cases were studied during the therapeutic administration of phenylhydrazine. In each case bilirubinemia, with an "indirect" van den Bergh reaction, resulted. In the cases of leukemia, on the other hand, the serum bilirubin was reduced in quantity and low values were the rule.

The bilirubinemia and jaundice observed in cases of hemolytic icterus, pernicious anemia, or following the therapeutic use of phenylhydrazine, is hemolytic in origin. It is therefore primarily a measure of the intensity of the hemolytic process rather than of disturbance in the functional activity of the liver. We recognize the possibility of an alteration in the hepatic threshold for the excretion of pigment which may be in part responsible for the bilirubinemia in these cases, but such an alteration, if present, should be considered as an accompaniment of the hemolytic process rather than evidence of direct hepatic damage.

Phenoltetrachlorphthalein—The phenoltetrachlorphthalein test was negative in nine of the twelve cases of pernicious anemia studied (fig 3). Marked retention of dye was present in one case (case 2) which was observed during the peak of a hemolytic crisis. The dye retention apparently should be related to the marked bilirubinemia for a slight degree of retention of dye was observed in three out of seven cases of hemolytic jaundice. Bilirubinemia was the most marked (44 to 77 mg) in these cases. The degree of retention observed in these cases was slight and contrasts with the observations previously reported in cases of obstructive jaundice in which the degree of retention of dye more closely corresponds to the degree of retention of bile and bilirubinemia.

In the cases of splenic anemia a retention of phenoltetrachlorphthalein was observed in eleven of nineteen cases studied. The determination of the extent of cirrhotic changes in the liver, wholly on the basis of the appearance of that organ at the time of operation, is manifestly impossible. Nevertheless, it is noteworthy that in those cases in which the

surgeon reported the most marked cirrhotic changes there was considerable retention of dye, while no retention was present in the cases in which the liver appeared to be normal. Retention of phenoltetrachlorphthalein in such cases is apparently an index to the extent of the changes in the liver. Four cases in the series showed a slight increase in the serum bilirubin above the normal level. In each instance this accompanied distinct retention of dye.

A normal response to the phenoltetrachlorphthalein test was obtained in the cases of polycythemia vera and leukemia.

COMMENT

These observations are of particular interest in the study of the relation between the serum bilirubin and the rate of blood destruction. That hemolytic jaundice is associated with an increased rate of blood destruc-

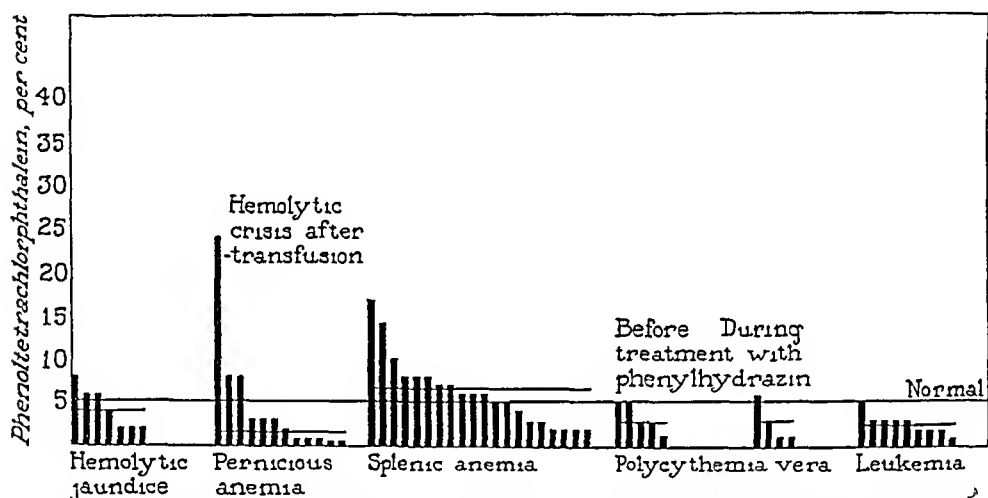


Fig 3—Variation in degree of phenoltetrachlorphthalein retention in different diseases of the hematopoietic system. The maximal normal level is indicated, and in each group the average value is shown by the horizontal line.

tion has long been recognized. That similar factors are active in pernicious anemia is increasingly evident.

The importance of the rate of blood destruction in maintaining the serum bilirubin is shown in the cases in which phenylhydrazine was given to reduce the number of erythrocytes. In these the hemolytic action of the drug was signaled by an increase in the serum bilirubin and by the appearance of hematin in the urine, and it was possible to follow the curve of hemolysis in this way. The similarity between the changes in these cases and in case 2 is striking. In the latter transfusion was followed by marked clinical evidence of hemolysis with jaundice and the appearance of bile in the urine. At the same time the serum bilirubin and the blood urea increased. The changes were transitory in nature and disappeared as soon as the products of the destruction of the erythrocytes were excreted.

The locus of origin of the bilirubin in cases of pernicious anemia and hemolytic icterus is important. The value of splenectomy in combating the effects of the latter disease is strikingly suggestive. Van den Bergh and Snapper³⁹ have examined the blood from the splenic artery and vein in a few cases and report the finding of more bilirubin in the venous blood than in the arterial. Rosenthal⁴⁰ and Lepehne³ studied single cases of hemolytic jaundice and splenic anemia and were unable to confirm this finding. Rich and Reinhoff⁴¹ more recently have reported a study of the serum bilirubin in a series of ten cases. In four the blood from the splenic vein contained more bilirubin than the control blood. Similar results have been reported by Kaznelson⁴². Our results shown in table 4 confirm this finding.

These observations strikingly confirm the clinical impressions concerning the activity of the spleen in destroying erythrocytes. They further emphasize the fact that the increase in the serum bilirubin in

TABLE 4—*Origin of Bilirubin in Hemolytic Jaundice and Splenic Anemia*

Case	Diagnosis	Bilirubin in Blood from		Difference, Mg for Each 100 Cc
		Splenic Artery, Mg for Each 100 Cc	Splenic Vein, Mg for Each 100 Cc	
1	Hemolytic jaundice	3.6	4.8	1.2
2	Splenic anemia	0.4	1.0	0.6
3	Splenic anemia	0.6	1.1	0.5

these cases is an index to the intensity of the hemolytic process and not to a pathologic disturbance in the functional activity of the liver. At the same time they should not be interpreted as evidence of an exclusive function of the spleen, for Mann and his co-workers have shown that jaundice will develop in dogs after the complete removal of the liver, spleen and other abdominal viscera, although bilirubinemia appears more slowly than in animals with an intact spleen. Recently Mann, Sheard, Bollman and Baldes⁴³ have been able to show by spectrophotometric methods that minute traces of bilirubin are normally and constantly

39 Van den Bergh, A. A. H., and Snapper, I. Ueber anhepatische Gallenfarbstoffbildung, *Berl klin Wchnschr* **21** 1081-1086, 1915.

40 Rosenthal, F. Untersuchungen zur Chemie des Blutes beim hamolytischen Ikterus mit besonderer Berücksichtigung der Lipoide, *Deutsches Arch f klin Med* **132** 129-178 (May) 1920.

41 Rich, A. R., and Reinhoff, W. F., Jr. The Bile Pigment Content of the Splenic Vein, *Bull Johns Hopkins Hosp* **36** 431-436 (June) 1925.

42 Kaznelson, P. Beitrag zur Entstehung des hamolytischen Ikterus, *Wien Arch f inn Med* **1** 563-574 (Aug) 1920.

43 Mann, F. C., Sheard, Charles, and Bollman, J. L. Studies on the Physiology of the Liver. XI, The Extrahepatic Formation of Bilirubin, *Am J Physiol* **74** 49-60 (Sept) 1925. Mann, F. C., Sheard, Charles, Bollman, J. L., and Baldes, E. J. The Site of the Formation of Bilirubin, *Am J Physiol* **74** 497-510 (Nov) 1925.

present in dogs' blood. These traces apparently arise chiefly in the bone marrow and spleen. Bioun and his associates³⁸ have especially emphasized the relation in pernicious anemia between the amount of serum bilirubin and the apparent activity of the disease. This phenomenon they interpret as evidence for the view that pernicious anemia is associated with increased destruction of blood. We are in entire accord with this view and wish again to emphasize the value of the estimation of the serum bilirubin in distinguishing between the primary or hemolytic anemias and certain secondary anemias, especially splenic anemia, or that associated with carcinoma.

The accumulation of an iron containing pigment in the liver in pernicious anemia is well known⁴⁴. Stieglitz⁴⁵ has emphasized the infiltration of the kidney with this pigment and suggested that disturbance in renal function may result from it. We have not been able to demonstrate a definite disturbance in the functional activity of the liver although marked morphologic changes have been described in consequence of the infiltration with pigment or fat. Bilirubinemia was present but this probably was the direct result of the hemolytic process. Proof that it is secondary to the changes in the liver is lacking.

SUMMARY

Functional disturbances in the liver are apparently not sufficiently great to be of clinical significance in most diseases of the hematopoietic system, hemolytic jaundice, pernicious anemia, polycythemia, leukemia or of splenomegaly of the Gaucher type. The greater number of tests for hepatic function studied did not show significant changes from the normal. Infiltration of the liver by iron containing pigments, fat or leukoblastic cells, has been described in these different conditions but if functional disturbances are produced by this infiltration they were not such in kind or degree as to be demonstrable in these cases by the methods studied.

An increase in serum bilirubin is of value in the differential diagnosis between hemolytic anemias and the ordinary secondary types. In cases of hemolytic icterus and pernicious anemia, changes in the serum bilirubin serve accurately to indicate changes in the severity of the hemolytic process. The serum bilirubin is equally of value in following the course of a hemolytic crisis after transfusion, or the artificial hemolytic crisis produced by the therapeutic use of phenylhydrazine. The serum bilirubin in these instances is an index to the severity of the hemolytic process rather than to disturbances in the liver.

44 MacCallum W. G. Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1916.

45 Stieglitz, E. J. Disturbances of Renal Function in Pernicious Anemia, Arch. Int. Med. 33: 58-70 (Jan.) 1924.

The "indirect" diazo reaction when associated with an increase in the serum bilirubin is characteristic of an icterus of hemolytic origin, and is of diagnostic value. The frequent association of gallstones with hemolytic jaundice will serve to account for the occasional "direct" diazo reactions obtained in the latter condition.

In cases of splenic anemia particularly the phenoltetrachlorophthalein test shows changes that may apparently be related to the severity of the cirrhotic changes in the liver. Under these conditions the test would seem to be of some diagnostic and prognostic value.

In cases of myelogenous leukemia, and to a lesser extent in those of lymphatic leukemia and polycythemia vera, there is a disturbance in the nonprotein nitrogen partition in the whole blood. This is characterized by an increase in the amino-acids and undetermined nitrogen fractions with a consequent increase in the total nonprotein nitrogen. These changes are perhaps to be related to the metabolic activity of the cells themselves and especially that of the leukocytes rather than to any general metabolic disturbance.

PERSISTENT PREMATURE CONTRACTIONS

A CLINICAL STUDY *

HAROLD L OTTO, M D

AND

HARRY GOLD, M D

NEW YORK

This article is a report of the results obtained in a clinical study of the premature contraction, with particular regard to its reaction to the drugs most commonly used in the treatment and study of heart disease

There are in the literature many references to the response of the premature contraction to drugs, as appendixes to studies of cardiac arrhythmias in which attention is given particularly to auricular fibrillation and flutter. This is especially the case in the recent work on the action of quinidine.

Edens and Huber ¹ and Wenckebach ² reported the action of digitalis on the premature contraction, but recorded impressions rather than the results of carefully controlled experiments.

The arrhythmia does not easily lend itself to careful study because of its inconstancy. Patients showing frequent premature contractions in great numbers over long periods of time are not often seen at the hospital. Approximately, one of every five patients with premature contractions in the cardiac clinic maintained them over sufficiently long periods of time while under observation there to make them suitable for purposes of study.

Considerable care was utilized in the selection of patients for this study. Patients were not considered as suitable unless there was no spontaneous disappearance of the premature contractions over a period of at least one month while under observation in the clinic.

METHOD

Each person selected for the study was admitted to the hospital and put to bed. At least three five minute electrocardiograms on a preferred lead, usually Lead II (this depended on the clarity of the

* From the third medical (New York University) division and adult cardiac clinic of Bellevue Hospital and the department of pharmacology, Cornell University Medical College.

1 Edens E. and Huber, J. E. Ueber Digitalisbigemmenie, *Deutsches Arch f klin Med* **118** 476 1916. Edens, E. Ueberdigitaliswirkung, *Deutsches Arch f klin Med* **104** 512 1911.

2 Wenckebach, K. F. The Effects of Digitalis on the Human Heart, *Brit M J* **2** 1600, 1910.

curve), were taken daily, approximately at 9 a m, 1 p m and 5 p m. These electrocardiograms were taken on bromide paper and yielded strips averaging about 30 feet long.

In the earlier cases five readings a day were taken, but later it was found that three were adequate, because the average of three readings a day differed little from the average of five readings a day.

Whenever the electrocardiograph was not available, clinical readings were taken. These were obtained by the observer with the stethoscope at the apex and his free hand recording with paper and pencil the number of normal beats between each premature contraction, thus, 3/2/6/5/4/2//1/2/, etc., the numerals representing the normal beats, the vertical lines, the premature contractions. If more than one occurred in succession the strokes were set down accordingly.

From each record the following facts were ascertained:

- 1 The total number of consecutive beats
- 2 The total number of premature contractions
- 3 The division of the premature contractions into right and left ventricular and auricular
- 4 The constancy of the "focus"
- 5 The heart rate
- 6 The pattern of the premature contractions, i e., the number of normal beats between premature contractions

The total number of beats, the total number of premature contractions and the heart rate were then used to determine the average number of premature contractions per minute over the period by simple proportion.

The results of the foregoing calculations made from the readings of each day were averaged and the figure obtained used as the average number of premature contractions per minute the individual had that day. Furthermore, where studies were made of drugs with transient effects, electrocardiograms were taken either continuously during the study, or every five minutes, hour, two hours, etc., as the case demanded. No medication was administered during the first seven days, the minimal control period, to fourteen days, the maximal control period in the hospital.

As already stated, these patients had been without medication for one month in the clinic prior to admission into the hospital. It was in view of the known inconstancy of the arrhythmia that this elaborate procedure was thought necessary.

From the accompanying table (table 1) of the patients used for the study, it may be seen that the group of twelve cases studied include patients of both sexes between the ages of 23 and 66 with practically

every common variety of heart disease, viz, rheumatic, syphilitic, arteriosclerotic, with and without hypertension, and those of "unknown" etiology with or without other evidence of heart disease. Such a variety of cases incidentally offered an opportunity to compare the response to various drugs, of the premature contraction occurring in the different types of heart disease.

TABLE 1—*The Cases Studied as to Etiology, Anatomy and Function**

Case	Sex†	Age	Predominant Type of Premature Contractions‡	Diagnosis	Condition			Further Comment	Result		
					At Time of Study	During Study	End of Study		Epinephrine	Quinine	Digitalis
1	♂	53	A	Syphilitic aortic dilatation and regurgitation	IIA	IIA	IIA		++ +	-- --	-- --
2	♀	48	A	Unknown, enlarged heart, hypertension	IIB	IIB	IIB		++ +	-- --	
3	♂	66	A	Arteriosclerosis and enlarged heart, hypertension	IIA	IIA	IIA	Died suddenly, cerebral hemorrhage	++ +	-- --	
4	♀	38	A	Rheumatic mitral stenosis and insufficiency	IIA	IIA	IIA		++ +	-- --	-- --
5	♂	26	V	Unknown, no other evidence of heart disease	I	I	I		++ +	-- --	-- --
6	♀	23	V	Unknown, no other evidence of heart disease	I	I	I		++ +	-- --	
7	♂	46	V	Unknown, double mitral and aortic disease	IIA	IIA	IIA		++ +	-- --	-- --
8	♂	56	V	Arteriosclerosis enlarged heart, hypertension	IIA	IIA	IIA		++ +	-- --	-- --
9	♂	46	V	Unknown, enlarged heart	III	IIB	IIA	Back in hospital 1 week later	++ +	-- --	-- --?
10	♂	55	V	Arteriosclerosis enlarged heart	III	IIB	IIB		++ +	-- --	-- --
11	♀	41	V	Arteriosclerosis, aortic insufficiency	III	III	III	Died three weeks later	++ +	-- --	
12	♂	46	V	Rheumatism mitral stenosis and insufficiency, intraventricular block	III	III	III	Died	++ +	-- --	-- --

* The variations of age and diagnoses should be noted.

† In this table, ♂ indicates male, ♀, female.

‡ A indicates auricular premature contractions, V, ventricular premature contractions.

All patients had clinical cardiac enlargement except two in whom ventricular premature contractions were the only evidence of heart dysfunction. One of the latter had had syphilis with intensive treatment some years before.

In table 1, the last three columns represent the relative degree of response of each patient to epinephrine, quinine and digitalis. The plus signs represent increase in the number of premature contractions occurring per minute; the minus signs represent diminution in the number of premature contractions occurring under the influence of the drug.

THE TYPE OF PREMATURE CONTRACTION

In any single case one type of premature contraction predominated. Thus, in four patients the premature contractions were predominantly auricular, in eight predominantly ventricular, and of the latter, in three predominantly right ventricular and in five left ventricular in origin. While one type predominated in each case, almost all at some time during observation showed auricular premature contractions if they were of the predominantly ventricular type or vice versa. And again, the patients with the ventricular type showing left premature contractions would at some time show right premature contractions and vice versa. This suggests that the causal factor of the premature contraction operates on both auricles and ventricles in the same heart even though it may show a marked preference for one or the other of the chambers.

PARASYSTOLE

In studying the relationship between the premature contractions and the normal beats, using the long strips of five minute electrocardiograms, no convincing evidence could be found in the strips examined that the premature contractions were responses to impulses belonging to a rhythmic series with a center of impulse formation independent of the sinus and functioning simultaneously with it. This is in accord with the findings of Iliescu and Sebastiano³. Strips were selected from our electrocardiograms, six with auricular and four with ventricular premature contractions. The following types were included:

- 1 Auricular premature contractions showing an apparently constant focus (in which the auricular aberrations signalling the inception of a premature contraction were all alike)

- 2 Auricular premature contractions which on superficial inspection appeared to be regularly recurrent

- 3 Constant auricular bigeminy and trigeminy

- 4 Ventricular premature contractions with constant focus

- 5 Ventricular premature contractions appearing to be regularly recurrent

- 6 Ventricular bigeminy and trigeminy

These were timed in one one-hundredth seconds, measuring the R-R interval, beat by beat in each, and checking over the P-R intervals to eliminate variation in auriculoventricular conduction as a source of error. While the comparator was not used in these calculations, they were accurate to at least the one-fiftieth second and, furthermore, any errors resulting because of not using it in making the calculations would only tend to strengthen the evidence for the hypothesis of parasystole, rather than the

3 Iliescu and Sebastiano Heart 10 102

reverse In no strip examined could any simple mathematical time relationship between the premature contractions be said to hold with the same constancy as in the normally beating heart In the strips showing bigeminy and trigeminy no simple time relationship was in evidence between the premature contraction and the normal beat preceding it If any rhythmic independent focus governs the production of the premature contraction, it is profoundly influenced by the normal contractions whenever they cross its time for recurrence for it usually was following a supposed "silenced response" that the greatest variations occurred

There was no evidence found to support the hypothesis of parasystole in the cases examined

REST IN BED

Rest in bed alone had absolutely no effect on the premature contractions quantitatively or qualitatively, i e, it did not lessen the number of the premature contractions per minute nor did it alter the focus, nor did it make a variable focus constant

HEART RATE

Below rates of approximately 100 per minute, the heart rate bears no relation to the number of premature contractions occurring per minute For example, a patient with a normal resting rate of 90 to 100 might have as many premature contractions per minute as another patient with a normal resting rate of 60 Furthermore, in any single patient there was no relation between the number of premature contractions per minute and the heart rate, provided the rate was below approximately 100 per minute After passing the rate of about 100, the number of premature contractions per minute tended to diminish and this diminution was in direct proportion to the rise in rate

Rest in bed had no effect on, and heart rate within the limits of 50 to 100 per minute had no relation to, the number of premature contractions prevailing

EFFECT OF EXERCISE

Exercise practically always increased the number of premature beats The usual effect was as follows While the rate was high, for the short interval following the exercise, the number of premature contractions were diminished or absent, but as soon as the rate fell below approximately 100 per minute the number of premature contractions were always increased and continued so for a short while thereafter It was common to see cases with auricular premature contractions develop some ventricular premature contractions following exercise and vice versa The diminution in the number of premature contractions immediately following exercise seems to be due simply to the rise in rate because in those patients in whom the exercise failed to increase

the rate to or above about 100 per minute, there was no diminution in the number of premature contractions

One patient (case 8, table 1) responded as all others during his control period. When full doses of digitalis removed the premature contractions none appeared following exercise to breathlessness. Three patients (cases 9, 11 and 12) were too sick to try exercise. Patient 1 responded as all others during his control period. Later, when practically free of premature contractions while under quinine, an increase in the number of premature contractions appeared following exercise.

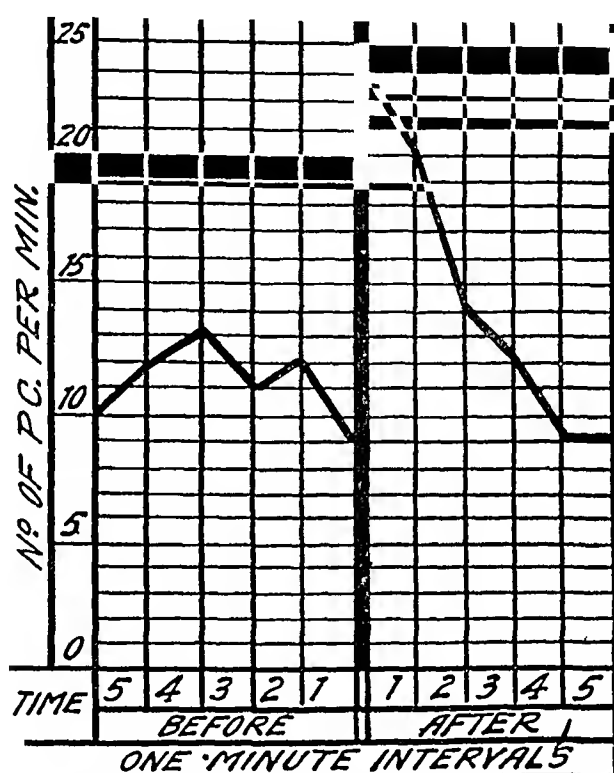


Chart 1—Effect of exercise

Chart 1 is a graphic representation of the effect of exercise on the number of premature contractions.

Table 2 is a random selection of the protocol figures of the study of the effect of exercise. In all there were thirty experiments done.

Following exercise, the number of premature contractions prevailing were increased.

EFFECT OF ATROPINE

Atropine was the first drug given following the control period. It was administered to all twelve patients. In six of them, a small dose, $\frac{1}{100}$ grain atropine sulphate was given first hypodermically. One hour later two doses each of $\frac{1}{30}$ grain were injected hypodermically twenty minutes apart. In the remaining six cases the preliminary small dose

TABLE 2—Effect of Exercise in Ten Experiments

	1		2		3		4		5		6		7		8		9		10	
	Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions		Preme- ture Contra- ctions	
	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.	Heart Calcu- lated	per Min.
One Minute Readings Before Exercise	90	26	70	19	80	12	66	22	54	10	58	8	54	9	62	1	58	4	54	10
	80	24	68	20	82	11	66	20	54	11	58	12	54	7	62	3	56	3	54	12
	80	21	68	18	80	12	64	22	52	10	58	10	54	8	62	2	56	4	54	13
	80	26	70	21	82	13	64	20	52	12	58	9	54	8	62	0	56	4	54	11
	70	24	70	19	80	11	64	21	52	9	58	10	54	7	62	2	58	3	54	12
One Minute Readings After Exercise	100	34	120	34	120	4	126	14	90	3	85	15	90	15	110	4	104	6	100	8
	96	38	100	36	100	13	100	30	78	20	78	15	63	24	80	13	76	11	80	23
	94	32	100	36	90	18	80	38	70	16	72	16	60	20	68	11	66	21	66	20
	90	26	90	33	80	19	74	38	66	16	72	10	60	18	62	9	64	19	66	14
	80	19	80	30	65	17	64	30	60	18	58	6	60	12	62	4	60	16	54	12

The heavy horizontal line in the center indicates the period of exercise

was omitted. Five minute electrocardiograms were taken every hour during the day of administration of the atropine.

The first small dose was given to produce the vagal stimulating effect and the second two doses to produce complete vagal paralysis. In this way, it was thought that a comparison between vagal stimulation and vagal paralysis might be brought out. Practically no evidence of vagal stimulation was obtained using the heart rate as the indicator.

Atropine had no effect on the number of premature contractions except in one patient (case 4, table 1) in whom the heart rate rose to 120 per minute and the premature contractions disappeared, the heart rate returning to 94 per minute in the next hour with the resumption of about the same number of premature contractions. This was in a patient with auricular premature contractions.

TABLE 3—*Effect of Atropine in Six Experiments*

	1		2		3		4		5		6	
	Premature Contractions per Min.		Premature Contractions per Min.		Premature Contractions per Min.		Premature Contractions per Min.		Premature Contractions per Min.		Premature Contractions per Min.	
	Heart Rate	Calculated	Heart Rate	Calculated	Heart Rate	Calculated	Heart Rate	Calculated	Heart Rate	Calculated	Heart Rate	Calculated
Five Minute Readings 1 Hr Apart Before Atropine	62	8	86	23	60	9	90	26	74	0	70	12
	62	3	86	19	60	6	88	24	72	0	70	14
	68	12	86	22	60	10	90	32	72	0	72	13
	66	20	86	18	60	7	90	31	72	0	70	13
Dose, grains	1/100		1/100		1/100		1/100		1/100		1/100	
½ hour after	60	8	86	22	52	7	80	34	72	0	68	14
Dose, grains	1/15		1/15		1/15		1/15		1/15		1/15	
Five Minute Readings 1 Hr Apart After Atropine	64	3	94	23	64	7	100	28	82	0	80	12
	60	6	100	21	68	12	120	0	104	0	100	15
	60	11	96	20	64	11	94	31	96	0	98	14
	60	8	100	18	60	13	90	30	96	0	96	15

In case 4 the absence of the premature contractions with the high heart rate and the absence of a definite effect following the drug in all should be noted.

All the patients given atropine developed other marked symptoms of atropinism, viz., dilated nonreacting pupils, dry, parched tongue and throat and some slight dizziness and mild delirium. Table 3 contains the protocol figures of the six atropine experiments with the preliminary small dose of the drug.

Atropine in full doses had no effect on the number of premature contractions prevailing, except when it produced a marked rise in the heart rate.

EFFECT OF EPINEPHRINE

A solution of epinephrine chloride, 1:1,000, was administered hypodermically in doses of 15 minims in eighteen experiments. Electro-

cardiograms of one minute duration were taken every five minutes during the study, usually five electrocardiograms before and five after the injection

The results were uniform. There was considerable increase in the number of premature contractions occurring per minute, beginning five minutes after the injection and lasting for thirty minutes to one hour. There was only a slight rise in the heart rate.

Patients with auricular premature contractions frequently developed ventricular premature contractions and vice versa. Patients with right ventricular premature contractions often developed left ventricular pre-

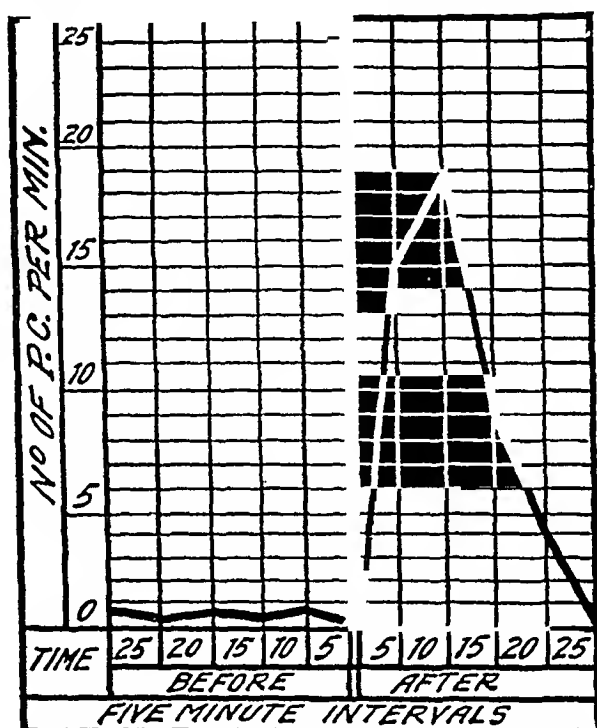


Chart 2—Good reaction following injection hypodermically of 15 minims of epinephrine

mature contractions and vice versa. Two premature contractions occurring together were not infrequent in the patients with ventricular premature contractions. In one patient with the ventricular type three premature contractions in series appeared frequently with the focus variable. In one patient with the auricular type, groups of four and five premature contractions in succession occurred.

Regular patterns of appearance of the premature contractions were frequent, where they were not in evidence before the injection. Thus trigeminy was common and short periods of bigeminy appeared in one patient with ventricular premature contractions (case 5 table 1). No

variation from the basic normal rhythm predominating ever occurred following the injection

One patient (case 1, table 1) with predominantly auricular premature contractions, while practically free of premature contractions under quinidine therapy, developed considerable numbers of them following the epinephrine and lasting for one hour and fifteen minutes

Another patient (case 8, table 1) with premature contractions of predominantly ventricular type reacted as all others with a marked increase following the epinephrine, but when free of premature con-

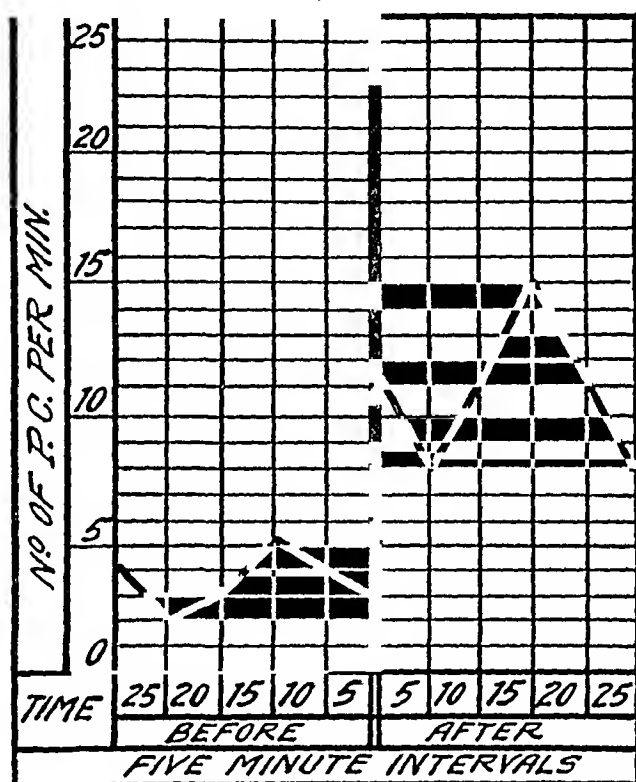


Chart 3—Poorest result in eighteen experiments of hypodermic injection of 15 minims of epinephrine

tractions during six weeks of digitalis therapy developed no premature contractions following another injection of epinephrine. Four weeks after the digitalis was discontinued no premature contractions had reappeared. Epinephrine injected at this time still failed to call forth premature contractions.

Table 4 contains the protocol figures of nine of the epinephrine experiments, and charts 2 and 3 contain the results of a slight reaction to epinephrine and a marked one, represented graphically.

Epinephrine increased the number of premature contractions prevailing

TABLE 4—Effect of Epinephrine in Nine Experiments

	1			2			3			4			5			6			7			8			9		
	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.	Heart Rate	Calcu- lated	Prema- ture Contra- ctions per Min.			
Before	76	11	3	94	3	70	0.5	62	6	100	36	100	22	76	10	96	19	56	0.1								
	78	17	2	94	2	70	0.1	66	7	100	40	96	21	76	5	90	17	53	0.2								
	78	14	3	94	3	70	0.5	64	7	100	37	96	22	76	6	90	18	53	0.5								
	78	16	3	96	3	70	0.5	64	7	100	35	96	22	76	5	90	20	53	0.2								
	77	10	3	92	3	66	0.5	64	7	100	36	96	19	76	6	90	19	53	0.1								
After	80	20	8	94	8	86	13	66	9	100	38	90	26	76	13	90	26	58	0								
	100	23	12	100	12	81	13	68	15	100	53	90	28	76	10	90	23	60	15								
	100	27	14	98	14	80	9	68	17	100	63	90	30	92	24	90	26	61	19								
	100	27	12	98	12	80	4	70	17	100	62	90	27	88	18	90	30	66	8								
	100	20	7	98	7	76	0.3	66	17	100	65	90	21	76	16	90	23	58	4								
										100	54							56	2								
																		58	0.6								

In each experiment five one minute electrocardiograms were taken five minutes apart before injection, the heavy horizontal line in the center indicates injection of epinephrine, 15 minims, hypodermically, following this five one minute electrocardiograms were taken five minutes apart

QUININE BY INTRAVENOUS INJECTION

Quinine dehydrochloride in solution of 1:30 was injected intravenously during a period of five to eight minutes into each of eight patients, four with auricular and four with ventricular contractions. Control electrocardiograms of five minutes' duration were taken at approximately two hours, one hour, one-half hour, and immediately before injection. In the first three cases, tracings were taken during the injection. In all cases, tracings were taken immediately after injection, and after approximately fifteen minutes, one-half hour, one hour,

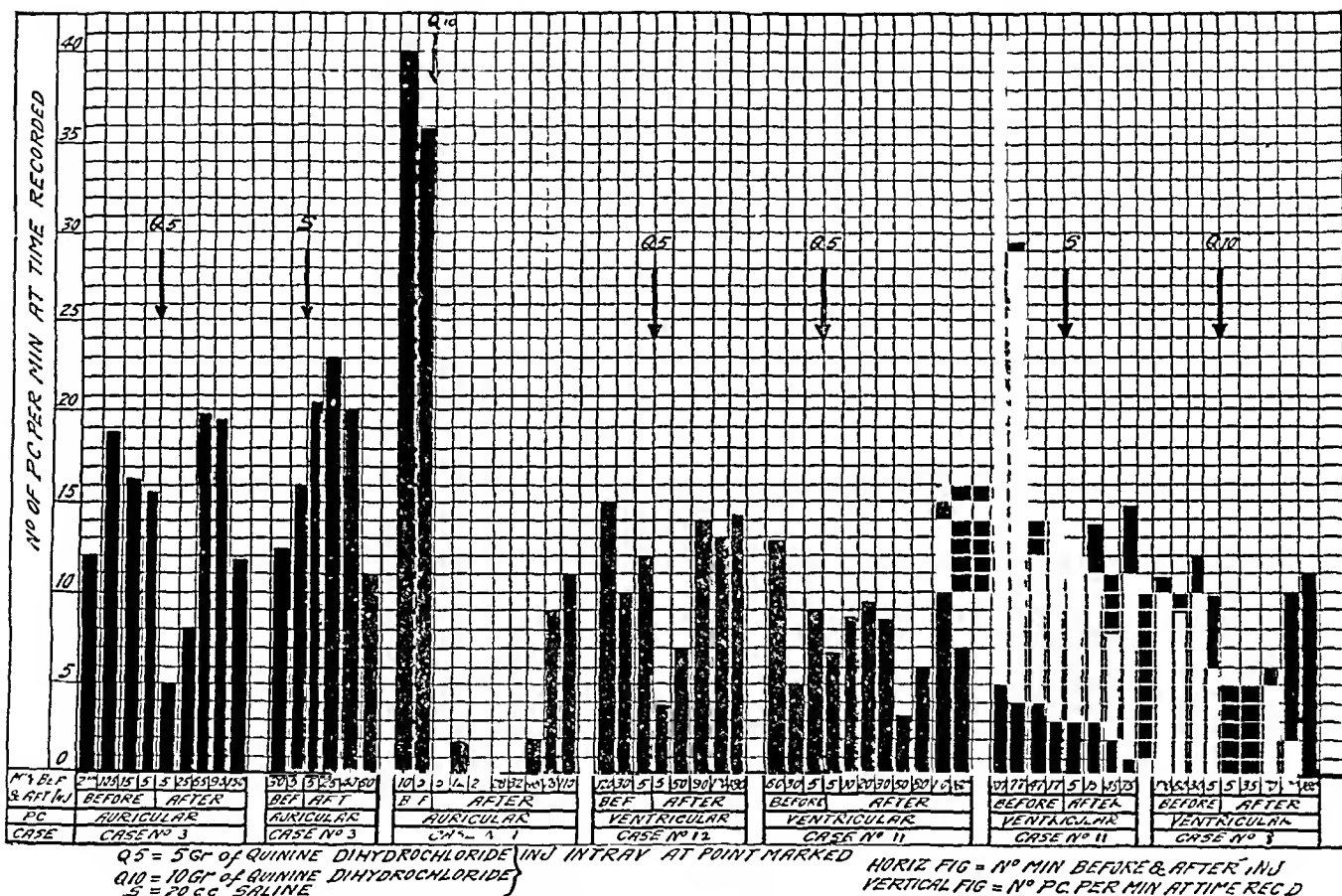


Chart 4—Effect of injection of quinine

two hours and three hours. In two instances physiologic sodium chloride solution was injected for purposes of control. It was without effect on the premature contractions and was therefore not repeated in the subsequent experiments. In the auricular group, two patients received 5 grains (0.32 Gm.) of quinine and two received 10 grains (0.65 Gm.). Of those given 5 grains, both showed marked diminution of the number of premature contractions per minute immediately following the injection. The effect had entirely disappeared within one hour.

Of those given 10 grains, one showed marked diminution in the numbers of premature contractions occurring (about 50 per cent), last-

There was no selective action observable in the effect of quinine on the various types of premature contractions, auricular, right ventricular or left ventricular

The manner in which the premature contractions were diminished was curious and worthy of mention. It was common to all. Chart 5 illustrates the point. Whereas before the injection, the pattern of the premature contractions was fairly constant, running for example 2/7/1/1/7/1/6/1/7/2/6/3/, etc., after the injection, the diminution of the total number of the premature contractions occurred principally by long periods of normal beats inserted into the original pattern, for

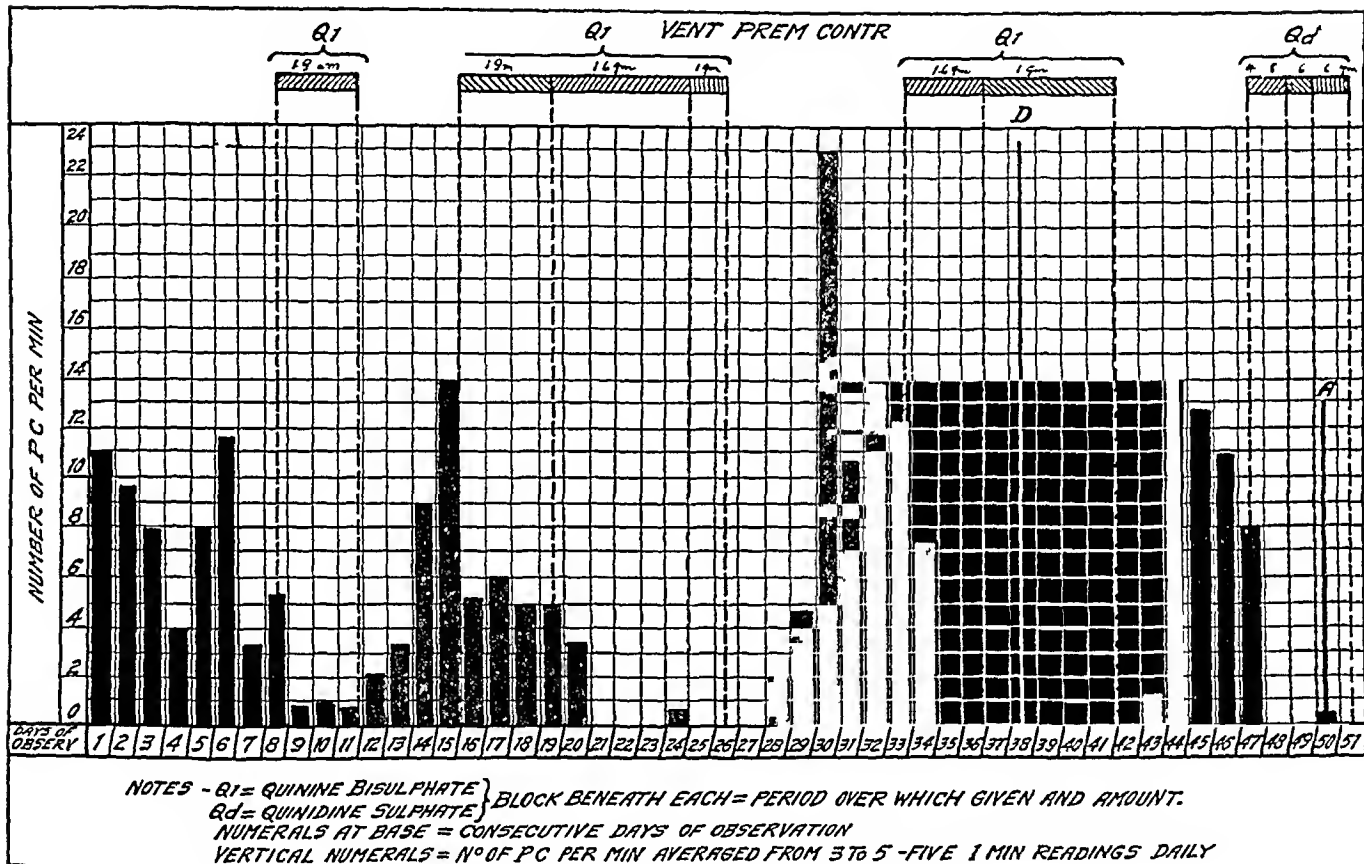


Chart 6—Effect of quinine in case 11

example, 7/1/6/1/50/80/7/6/70/6/1/, etc. It never occurred by a uniform change in the pattern, for example, 15/15/14/12/18/17/15/, etc. Chart 4 illustrates the reaction to quinine by intravenous injection.

In eight patients in whom quinine was injected intravenously, premature contractions were abolished in two, diminished in five and unaffected in one.

QUININE BY MOUTH

Following the intravenous injection of quinine dihydrochloride, the bisulphate was always administered by mouth in doses of 0.3 Gm. starting with two doses daily and increasing to three, then four, a total of

1.2 Gm a day In every case the dose was increased until premature contractions disappeared or symptoms of cinchonism supervened It was administered to twelve patients, four with auricular premature contractions and eight with ventricular premature contractions

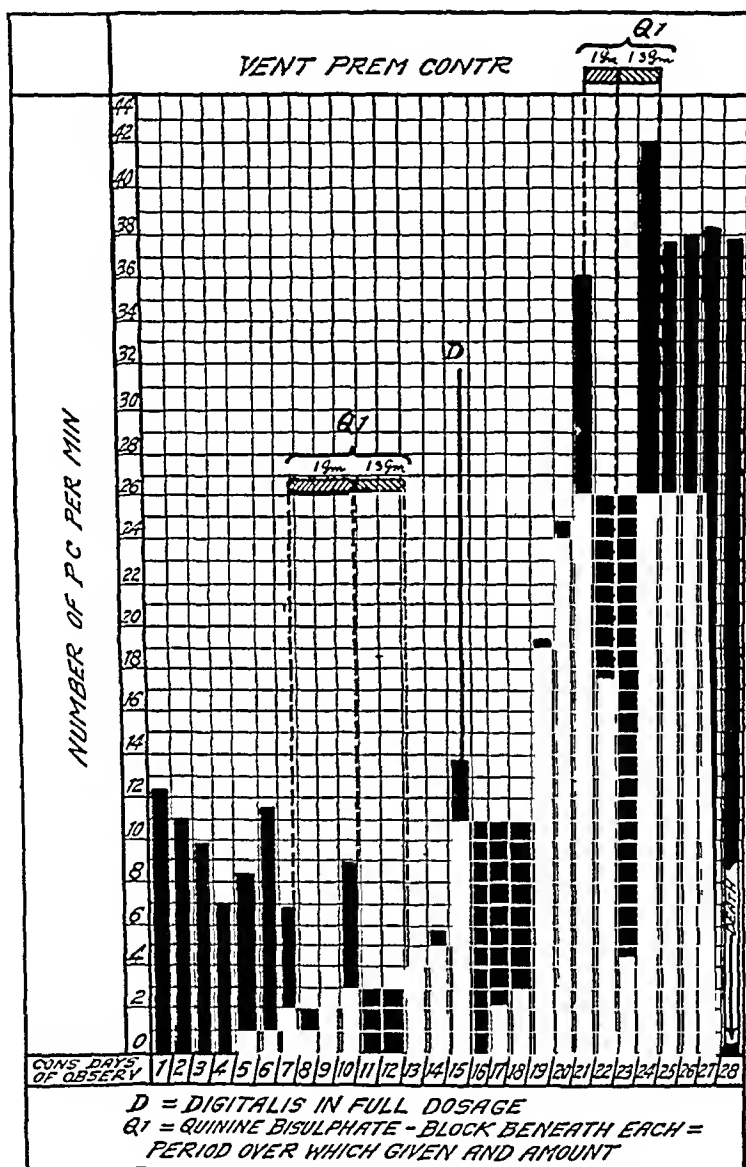


Chart 7—Effect of quinine by mouth in case 12

Among the four with auricular premature contractions, three had considerable diminution of the total number of premature contractions per day In one of these (case 3, table 1), a very great diminution occurred the first day, followed by a gradual increase in their number, in the succeeding days without ever reaching the original level The same was true of the other two to a lesser extent In the fourth

patient (case 1, table 1) complete abolition of the premature contractions occurred and was maintained by 0.3 Gm three times daily. This continued for two weeks, after which time the premature contractions began to appear in varying numbers. The dose was raised to 0.3 Gm every four hours, which again abolished them, but tinnitus supervened after three days on this dosage and the drug had to be discontinued. Subsequent administration of 0.3 Gm three times daily produced a marked diminution but there was a distinct tendency toward a gradual increase in the number of premature contractions despite the continued administration of the drug ("escape").

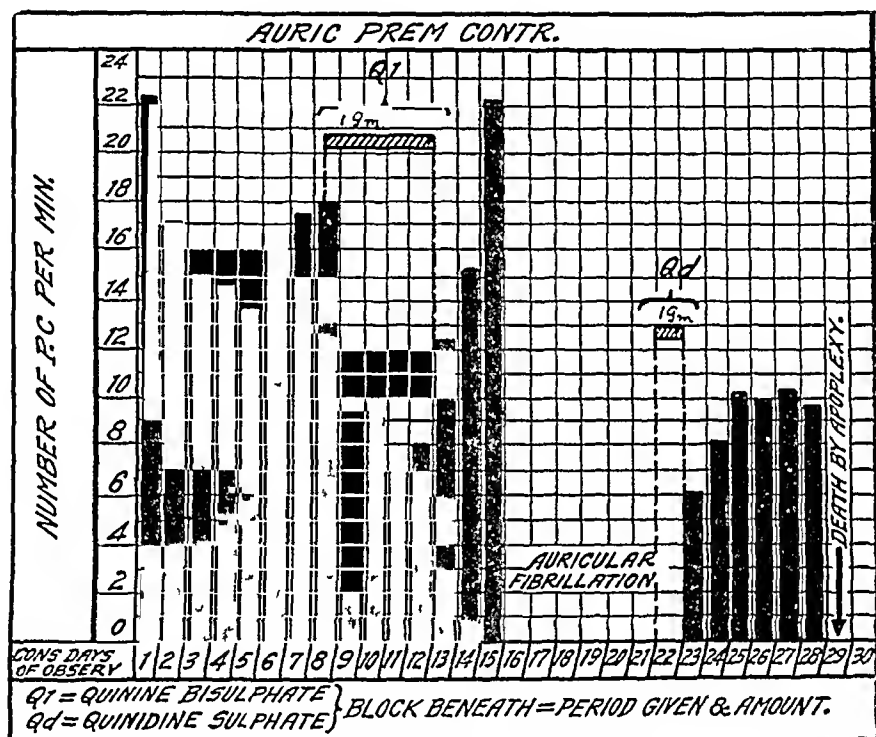


Chart 8—Effect of quinine and quinidine by mouth in case 3

Among the eight patients with ventricular premature contractions, in only one case (case 11, table 1), of arteriosclerosis with a hopeless prognosis, did quinine abolish the premature contractions entirely. In this patient administration and withdrawal was tried three times and in all the results were the same, although at different times the same dose was not equally effective.

All other cases showed diminution in the number of premature contractions to varying degrees, with the characteristic tendency to "escape" being always present. Increasing the dosage, which was done in all until symptoms of cinchonism appeared, repeated the foregoing phenomenon. In those patients with failure no improvement of the circulation occurred.

The two patients showing complete disappearance of the premature contractions under this therapy stated that they felt better, because the annoying "jumping of the heart" had disappeared

Charts 6, 7 and 8 illustrate samples of reaction while under quinine therapy

Quinine administered by mouth reduced or abolished the premature contractions in the patients observed

QUINIDINE BY MOUTH

Quinidine was given in doses beginning with 0.2 Gm twice daily and increasing to once every four hours as the case demanded. The results with quinidine differed from those with quinine only in the fact that

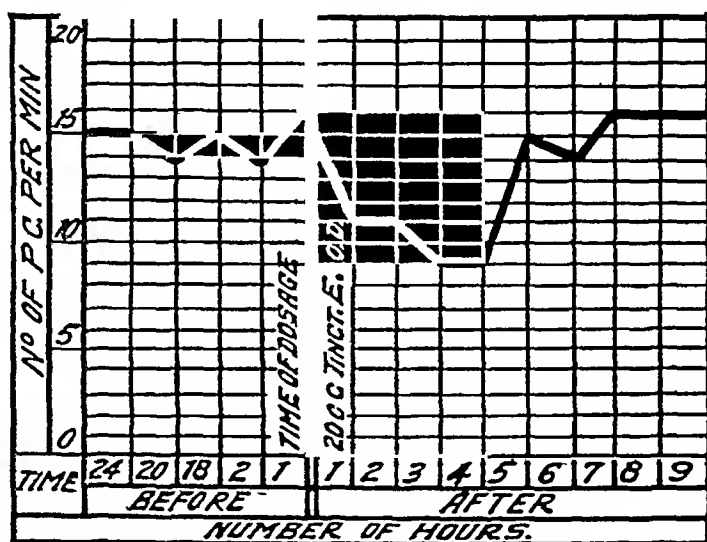


Chart 9—Effect of digitalis in full dosage in case 7, case 9 gave practically the same results

quinidine was more potent in reducing the number of premature contractions. In cases in which quinine entirely abolished them, quinidine did likewise, in cases in which quinine diminished them quinidine did so to a greater degree than the quinine. Likewise the characteristic "escape" of the premature contractions from the influence of the drug was less in degree.

Quinidine administered by mouth reduced or abolished the premature contractions

EFFECT OF DIGITALIS

The eight patients studied were given from 0.1 to 0.15 of a cat unit of the tincture of digitalis per pound of body weight in one or two doses, and three cat units per day thereafter. During the day of the full digitalization electrocardiograms of five minutes' duration were taken hourly.

There were two patients with predominantly auricular and six with predominantly ventricular premature contractions

Of the two patients with auricular premature contractions, one (patient 1, table 1) showed practically complete disappearance of the premature contractions following the administration of the digitalis, and continued so during the entire time of exhibition of the drug. Withdrawal resulted in the gradual return of the premature contractions to the original number. Readministration in the same way yielded the same result. In this patient, digitalis was unintentionally administered to minor toxic symptoms (nausea and vomiting). No increase in the

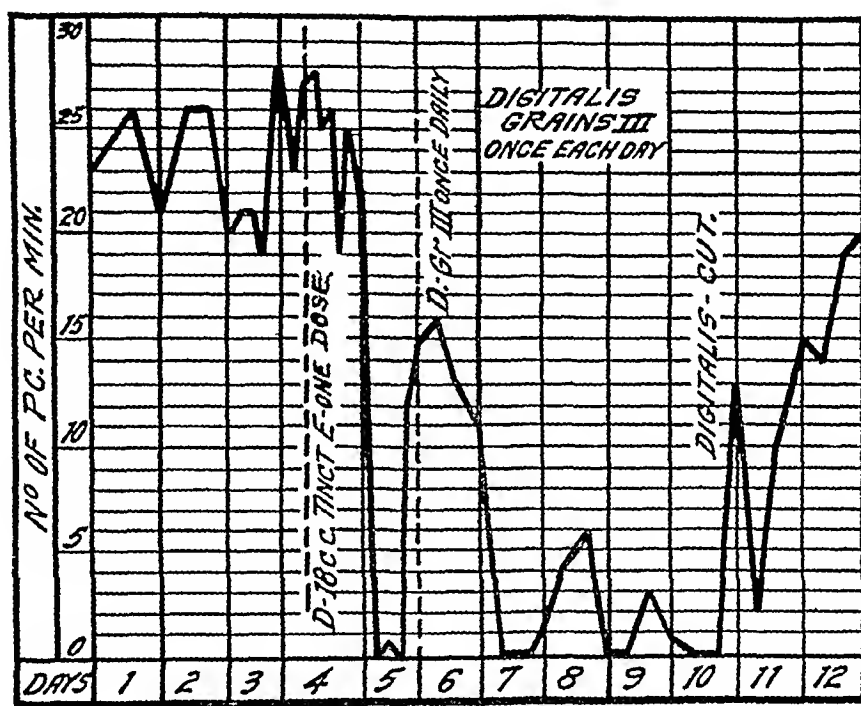


Chart 10—Effect of digitalis in full dosage in case 4

number of premature contractions occurred. In the other patient (case 4, table 1), digitalis so given caused a marked diminution in the number of premature contractions.

Among the six patients with ventricular premature contractions, two (cases 5 and 8, table 1) showed complete disappearance of the premature contractions following the administration of the drug. In one of these (case 8, table 1), made the subject of a separate report, this was studied in detail and repeated twice.

In two other patients, both terminal (cases 11 and 12, table 1), a very marked increase in the number of premature contractions appeared about twelve hours after administration of the drug, this occurring at one observation only (in charts 6 and 7, marked *D*, in chart 6 also comparative epinephrine reaction, marked *A*, should be noted). The

observation has not been repeated since and the question as to whether it resulted from the digitalis or was coincidental cannot be decided. In one of these (case 11), this occurred while free of premature contractions under quinine (this patient is not included in the digitalis series because of the simultaneous quinine administration). The other patient showed marked but temporary diminution following the increase. This lasted for two days and was again followed by a marked increase in the number of premature contractions until death six days later.

One patient (case 10, table 1) showed considerable diminution. In the remaining two patients digitalis had no noticeable effect (chart 9). Charts 9, 10 and 11 illustrate the types of reaction to digitalis.

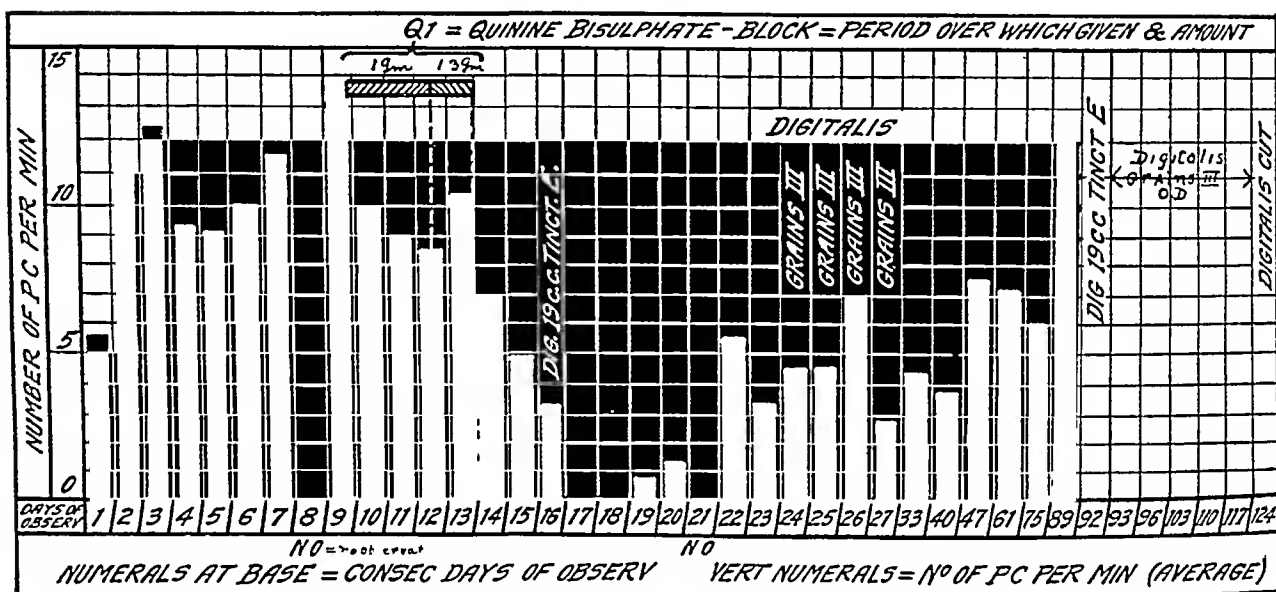


Chart 11 —Effect of digitalis in full dosage in case 8

Digitalis in large doses caused diminution to complete disappearance of the number of premature contractions present in six of eight patients studied.

SUMMARY AND COMMENT

In general rest in bed and atropine had no effect on the number of premature contractions. Exercise and epinephrine increased the number. Quinine, quinidine and digitalis decreased the number. These results appeared to be qualitatively, but not quantitatively, constant and unrelated to the type of the premature contraction or the etiologic, anatomic or functional type of heart disease in which they occurred. This represents only a small group of patients. Whether a relationship between these factors does exist remains for further study to establish.

References are commonly made in the literature to the beneficial effects of the withdrawal of coffee, tea, tobacco, alcohol, etc., in patients

with premature contractions. Undoubtedly such measures do diminish or abolish the premature contractions in certain cases. There is, however, a large group of patients in whom such measures are without effect. In the latter group, there is recourse to quinine, quinidine or digitalis. Quinine appears to be the least satisfactory because of the large dosage necessary and the early supervention of cinchonism. With quinidine the results are better but the tendency of the premature contractions to "escape" demands increasingly larger doses. The results of our studies indicate that both of these drugs have a limited field of usefulness in the treatment of patients with premature contractions and, furthermore, that digitalis deserves a more prominent place in the treatment of the premature contraction than it has heretofore received. A careful study of our records indicates in nearly all cases there was a considerable reduction in the number of premature contractions or their total abolition at some time during its administration. To obtain more satisfactory results with digitalis appears to be largely a question of proper dosage. A study along these lines is at present in progress.

THE RATIONALE OF THERAPEUTIC PUNCTURE IN PERICARDIAL EFFUSIONS

AN EXPERIMENTAL STUDY †

CHARLES SPENCER WILLIAMSON, M D

AND

HAROLD N ETS, M S

CHICAGO

Are patients with pericardial effusions aspirated early and often enough? Are patients with simple serous effusions permitted to die as the result of increasing intrapericardial pressure because of the lack of aspiration? If these two questions are answered in the affirmative why do we fail so often to institute this remedial measure?

We raise these questions because in the last few years one of us (C S W) has had under his direct observation four cases of pericarditis with effusion of a simple serous character in which, according to his best judgment, life might have been saved if aspiration had been employed. To justify this statement a brief synopsis of these cases is here given.

REPORT OF CASES

CASE 1—I was called late in the forenoon by my intern at the hospital who stated that a patient had been admitted the night before with what he believed to be a pericardial effusion. A to-and-fro rub was audible all over the front of the heart, but I was told over the telephone that the signs of effusion were definite. Knowing my interest in this disease he asked me if I would come over to see the patient. The patient's pulse, I was told, was fairly good and he thought there was no impending danger. I arranged to see the patient that afternoon. At perhaps 1 p. m. I was again called to the telephone and told that the patient's pulse had grown very much weaker within the previous half-hour. I left for the hospital immediately, found the situation to be exactly as represented and was preparing to do a puncture when the patient suddenly died. This is the patient referred to in a previous article as experiment 27¹. We aspirated all the fluid we could obtain a few minutes after death and immediately injected the same amount namely 270 cc., of agar solution. After this had thoroughly hardened the pericardial sac with the great vessels were removed and a cast made of them. It may be noted that the total amount of the exudate, as determined by the measurement of the cast by the displacement method, was 405 cc. This case is a peculiarly instructive one in that the pressure conditions were precisely the same as during life. From an inspection of the cast of the heart the great veins and auricles especially were seen to be flattened out and this must have been their condition in the last moments of life. As was said in the previous study, one cannot help but believe that death in this case was actually the result of extensive pressure and that had the fluid been aspirated the pressure factor at least would have been removed.

* From the department of medicine of the University of Illinois College of Medicine.

1 Williamson, C S. Pericarditis with Effusion. *Arch Int Med* 25:222 (Feb) 1920.

CASE 2—A patient with a small right lower lobar pneumonia was seen in consultation. The patient did very well, so well in fact that a second consultation, which had been arranged for a few days later, was deemed by the attending physician to be unnecessary. Some days later I was summoned in great haste to take the first train to see the patient again. As he lived in an adjoining state, I was three or four hours in reaching him. On my arrival I obtained the following history. The temperature had been normal, or approximately so, for some days, but the patient had been developing considerable dyspnea. The family physician had considered that he was dealing with a greatly dilated heart. The pulse had been good until about an hour before I had been sent for, when it had suddenly become much weaker and this was the immediate reason for my having been summoned. A roentgenogram of the heart had been taken a few hours before and a few moments' study of it was sufficient to make an almost positive diagnosis of a moderately large pericardial exudate. Proceeding to the patient's room I found him in extremis and death ensued while a needle was being sterilized to puncture the pericardium. As there was some skepticism as to the correctness of the diagnosis, we proceeded as if the patient were still living and punctured the sac, with the result that a slightly turbid fluid under very high pressure spurted out of our needle. A necropsy was not permitted, but the velocity of flow was so great as to leave no doubt as to the degree of pressure in the sac.

CASE 3—This patient had a simple serous pericardial exudate following a severe tonsillitis and rheumatic fever. The fluid accumulated with considerable rapidity and it became evident that the intrapericardial pressure was rapidly increasing, since the dyspnea was growing greater and the blood pressure steadily going down. Permission to aspirate the pericardial sac was refused and a consultation with a colleague was insisted on and arranged. A few hours later the exitus lethalis occurred rather suddenly. Permission to examine the heart was obtained and disclosed about 500 cc of a serofibrinous exudate. Aside from a beginning verrucose endocarditis of minimal extent there were no significant postmortem findings.

CASE 4—This patient was a boy, aged 18, who went to the hospital with a temperature of 101 and with some substernal pain. He had just recovered a week or two before from a severe case of polyarthritides and tonsillitis. The remainder of the history was unimportant. Physical examination on the first day left us in doubt as to the actual existence of an effusion, but this doubt was quickly dispelled the next day when it became plain that not only was fluid present but present also in considerable quantity. A roentgenogram taken about thirty-six hours after admission was characteristic. The patient's general condition was fairly satisfactory. On admission the pulse rate was 120 and the blood pressure about the same. The patient was shown in clinic to have a typical pericardial effusion and a second roentgenogram showed a much larger exudate than before. It was then decided to aspirate as the blood pressure was beginning to fall and the patient had grown very dyspneic. My interns, who carried out the aspiration, removed only 250 cc and another roentgenogram taken a few hours after the aspiration showed little change in the outline of the effusion. The patient apparently improved markedly, but some days later died suddenly and unexpectedly. As a necropsy could not be obtained it cannot be stated with certainty just what the conditions were. It is, however, a fair question whether if more fluid had been removed the first time, or if a second puncture had been made, the pressure might not have been sufficiently relieved to make recovery possible.

In our opinion the characteristic thing about the deaths of these patients is that they occurred suddenly. All were supposed to be in fairly good condition, as judged by the usual clinical criteria, and yet shortly after they died. This type of death may be conveniently referred to as the pericardial death and occurs only or principally in such cases as are substantially uncomplicated.

A study of a number of accessible records, principally from the Cook County Hospital, disclosed briefly the following facts. Among fifty-four fatal cases of pericarditis with effusion there were nine in which no puncture was carried out and in which it seemed reasonable to believe

TABLE 1—*Experiment E*

Dog 11, weight, 12 Kg Nov 24, 1925

Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
10 30	0	-5	60
10 30 24	10	-5	60
10 30 54	14	-3	54
10 32 12	40	+1	50
10 33 18	48	11	30
10 34 06	58	23	18
10 34 48	66	29	6
10 35 24	76	37	-2
10 36 36	0	Clot	50

TABLE 2—*Experiment D*

Dog 11, weight, 12 Kg Nov 24, 1925

Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
9 05	0	-5	55
9 06	4	0	55
9 07	6	29	60
9 08	14	33	60
9 08 36	22	39	50
9 09 24	26	43	45
9 10 06	30	49	35
9 10 54	34	59	25
9 11 42	44	69	15
9 12 30	50	79	0

Some of the tracings did not reproduce well, but they can readily be reconstructed from the data in the tables

TABLE 3—*Experiment F*

Dog 11, weight, 12 Kg Nov 24, 1925

Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
10 15	0	-2	50
10 16	16	-13	50
10 17	34	-13	50
10 19 42	46	33	40
10 20 54	58	53	26
10 21 30	70	63	16
10 22 24	84	81	10
10 23 18	94	87	0
10 24 18	108	101	-8
10 25 42	0	47	100
10 27 12	0	30	80

that by this procedure life might surely have been prolonged and possibly or even probably rescued. In four other cases it would have probably been of great benefit, if not life saving. If these conclusions are even approximately correct it seems clear that we clinicians have

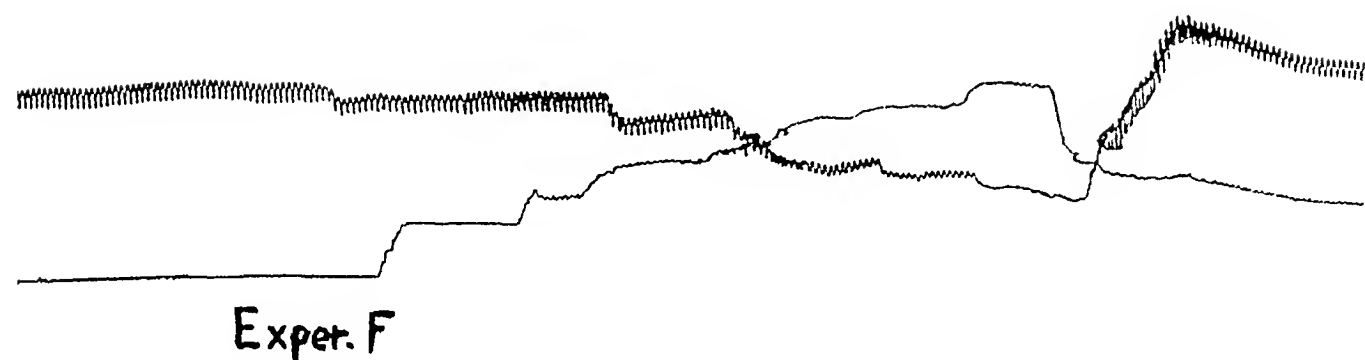


Fig 1—Experiment F

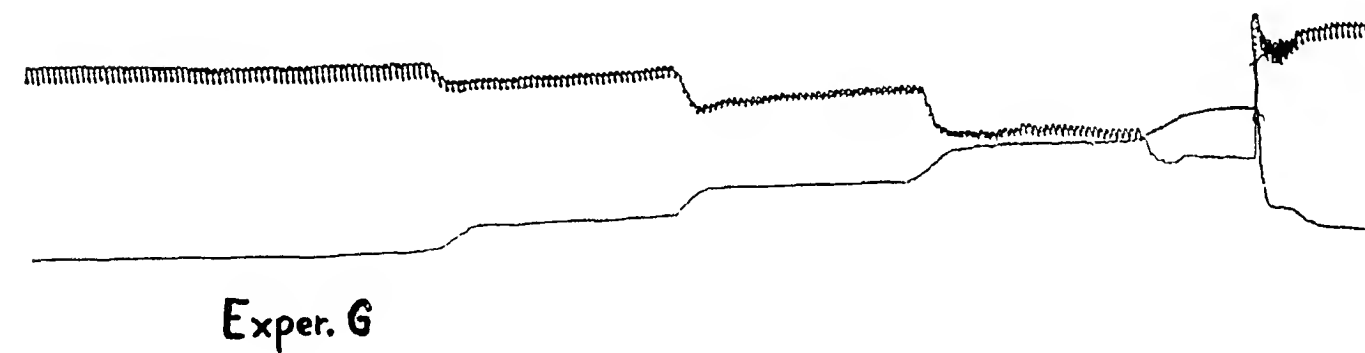


Fig 2—Experiment G

been permitting patients with pericardial effusion that has been correctly diagnosed to die for the lack of a timely carrying out of a simple therapeutic procedure

Practically all writers on this subject from François Franck to the present time are unanimous in the opinion that the circulation comes to

TABLE 4—*Experiment G*

Dog 12, weight, 10 Kg Nov 25, 1925

Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
11 15	0	-8	75
11 17 30	22	-6	75
11 19 48	40	12	65
11 22 12	60	32	45
11 24 12	76	52	15
11 25 12	82	70	5
11 26 24	0	-8	80

TABLE 5—*Experiment H*

Dog 12, weight, 10 Kg Nov 25, 1925

Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
11 10	0	5	55
11 11 24	20	3	55
11 14 06	40	13	50
11 15 18	62	33	45
11 16 12	78	51	20
11 17 48	88	62	8
11 18 54	98	78	-4
11 19 48	110	88	-8
11 21	0	-5	+75
11 21 48	0	-5	60

TABLE 6—*Experiment I*

Dog 12, weight, 10 Kg Nov 25, 1925

Time	Pericardial Pressure Mm Water	Venous Pressure Mm Water	Arterial Pressure, Mm Mercury
9 25	0	-2	45
9 27 06	20	10	45
9 28 36	42	24	35
9 30 06	66	44	7
9 31 54	78	58	-7
9 33 24	88	66	-15
9 34 24	100	74	-20

The pericardial cannula was 10 cm above the table and the leveling bulb 30 cm above when the heart stopped

an end at the instant when the intrapericardial pressure equals that in the cavae. Indeed, this would seem almost self-evident. While this is, comparatively speaking simple enough to understand in the experimental animal, we have no clinical means at our disposal to measure the intrapericardial pressure and have therefore no means of knowing when this begins to approximate the pressure obtaining in the cavae, since this

is in reality the real guide for therapeutic puncture. In the cases cited a correct interpretation of what was going on in the pericardial sac might have saved the patients' lives. Our study was undertaken to determine the relations between arterial, venous and intrapericardial pressures in animals with artificial pericardial effusions hoping thereby to gain additional points of prognostic and therapeutic value.

CONDITIONS OF EXPERIMENT

Dogs were used and under light ether anesthesia tracheotomy was performed and a cannula inserted into the right carotid artery and another into the left external jugular vein in such a manner that the

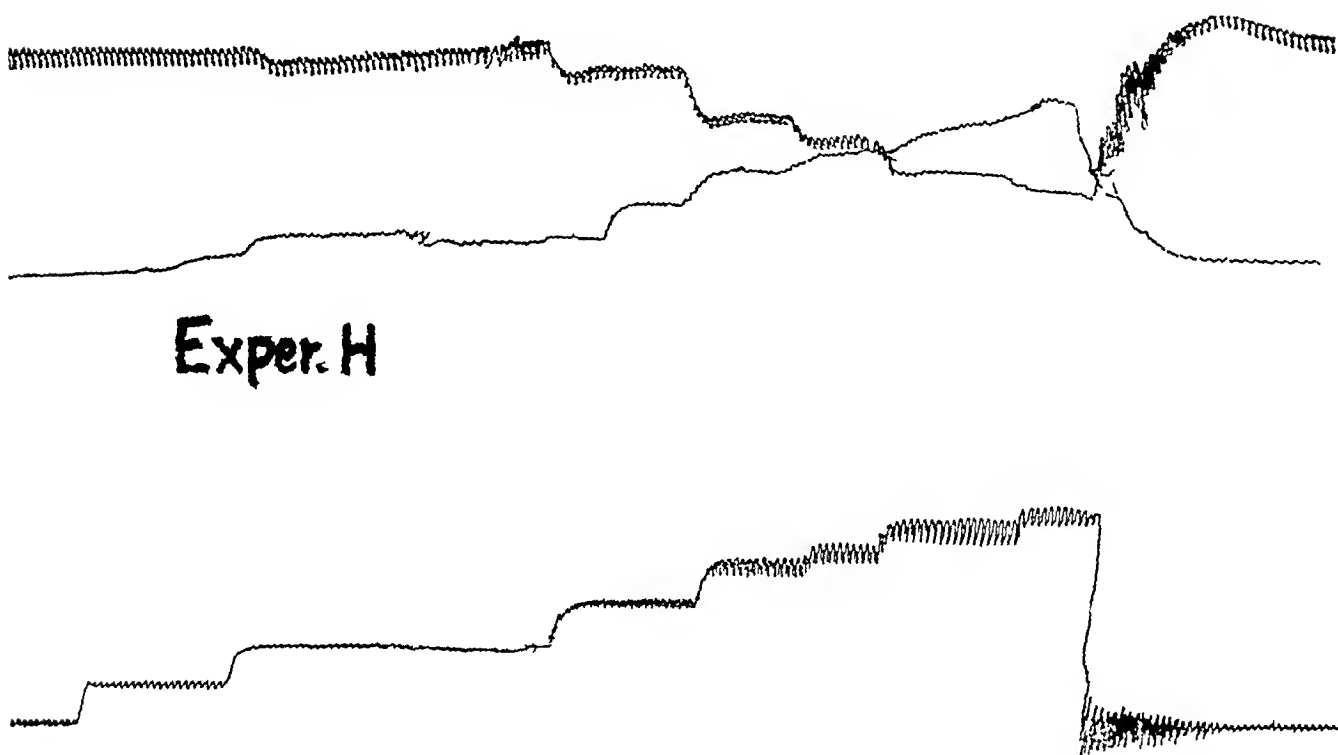


Fig 3—Experiment H

arterial and venous pressure changes could be recorded by means of manometers writing on a smoked drum. A vertical incision was next made between the ribs on the left side and the heart exposed, artificial respiration being instituted as soon as the thoracic cavity was opened. A T tube cannula was then tied into the pericardium and connected with a manometer writing on the smoked drum and also with a leveling bulb. Warm physiologic sodium chloride solution was used to produce pressure in the pericardium and this pressure could be regulated by means of the leveling bulb. Water was used in both the pericardial and venous and mercury in the arterial manometer. It should be noted that the venous cannula was tied in the vein centrally, so that the venous pressures recorded are not exactly comparable to those which might be taken clinically.

Each experiment was begun by recording the arterial and venous pressure before raising the intrapericardial pressure. The latter was then gradually raised by elevating the leveling bulb until it became so great that the heart stopped. At this point the bulb was quickly depressed so that the intrapericardial pressure was reduced to zero and

TABLE 7—*Experiment J*

Dog 13, weight, 15 Kg Nov 27, 1925

Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
9 40	0	11	50
9 41 19	4	11	50
9 42 38	6	11	50
9 44 38	14	13	50
9 48 14	22	13	50
9 50 56	26	21	45
9 54 32	34	28	35
9 57 32	40	40	-15
10 00 02	0	15	+35

TABLE 8—*Experiment K*

Dog 13, weight, 15 Kg Nov 27, 1925

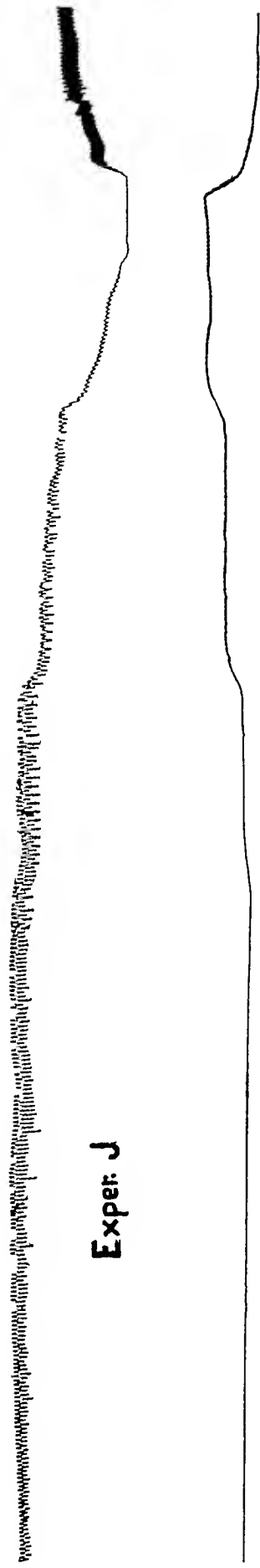
Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
10 46	0	-6	75
10 47 24	10	-6	75
10 49 30	20	-6	75
10 51 36	25	+10	75
10 54 24	30	16	70
10 56 24	35	24	65
10 58 24	45	36	45
10 01 48	50	52	-15
10 03 24	0	4	+65

TABLE 9—*Experiment L*

Dog 13, weight, 15 Kg Nov 27, 1925

Time	Pericardial Pressure, Mm Water	Venous Pressure, Mm Water	Arterial Pressure, Mm Mercury
10 07	0	-5	75
10 08	8	15	75
10 09	12	15	75
10 10 36	18	17	70
10 12 48	26	23	64
10 15 24	34	31	64
10 18 36	44	41	54
10 20 30	52	51	44
10 22 06	58	57	14
10 25	60	71	-20
10 27	0	23	+50

in each case the heart again quickly resumed its action. In each experiment the increase in pericardial pressure caused a steady rise in the venous and a steady fall in the arterial pressure. A time mark at six second intervals on the tracing enabled the recording of the time relations during the experiment. It is to be further noted that in a few of



Exper. J

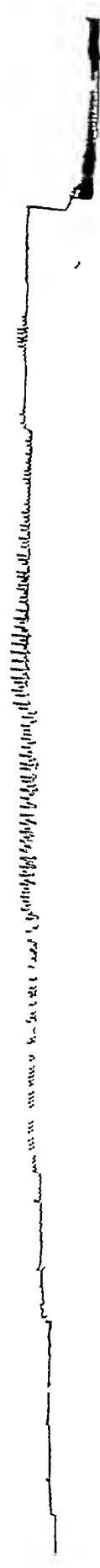
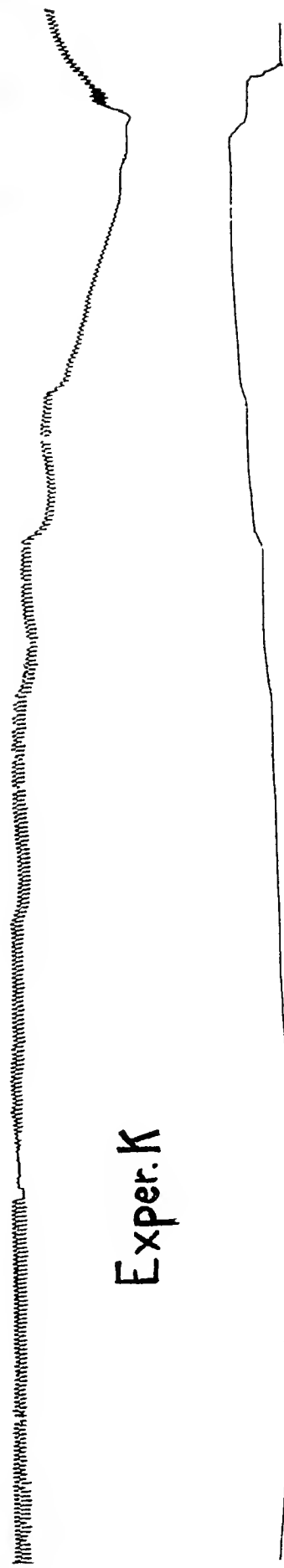


Fig 4—Experiment J



Exper. K



Fig 5—Experiment K

these experiments the incision over the heart was closed and the dog respired naturally, *i. e.*, without artificial respiration. As no difference was noted in these experiments artificial respiration usually was employed.

RESULTS

An inspection of the tables and the tracings shows that under our conditions of experiment a rather gradual raising of the intrapericardial pressure has for its invariable result the raising of the venous and the lowering of the arterial pressure. It will be further seen that for a given increment in the pericardial pressure these changes are more pronounced as this pressure becomes higher, so that as it approximates that which obtains in the vena cava, *i. e.*, as it nears the point at which the circulation stops, the rise in the venous and the drop in the arterial pressure is more noticeable. That these phenomena are due to the increase in pericardial pressure alone is evident from the fact that even a partial release of it causes the venous pressure to drop and the arterial to rise immediately. In these respects our results are entirely in accord with those of other authors. If now we turn our attention to the more quantitative pressure relations it is obvious that the first slight increase in pressure produces insignificant changes on either the venous or arterial side. Further increase in the pressure in the pericardium produces a fairly steady drop on the arterial and a corresponding rise on the venous side and the latter changes are accentuated as the critical point, *i. e.*, the point at which the circulation would stop is approached. We have already noted that our venous pressures, while not strictly comparable with the venous pressures as they might be taken clinically in an arm vein, would be roughly proportional to the latter.

If now we translate our findings into clinical practice it would seem that the following statements are justified. Measurements of the arterial pressure as carried out at the bedside enable one in a general way in cases of pericarditis, substantially uncomplicated, to prognosticate an increasing pressure in the pericardium. A steady fall in the arterial pressure, and especially a sudden increase in the rate of fall, indicates a near approach of the critical point, and calls for a therapeutic puncture. A steady rise in the venous pressure would enable the observer to predict the same event, but this is rarely done clinically, and its measurement is subject to a considerably greater error than the measure of the arterial pressure.

To make our points more clear, we append a number of tracings. In most instances, more than one tracing was taken from the same animal showing that the increase of pressure to a point sufficient to stop the heart is quite compatible with at least temporary recovery. The tables have been constructed from data read off from the tracings. While

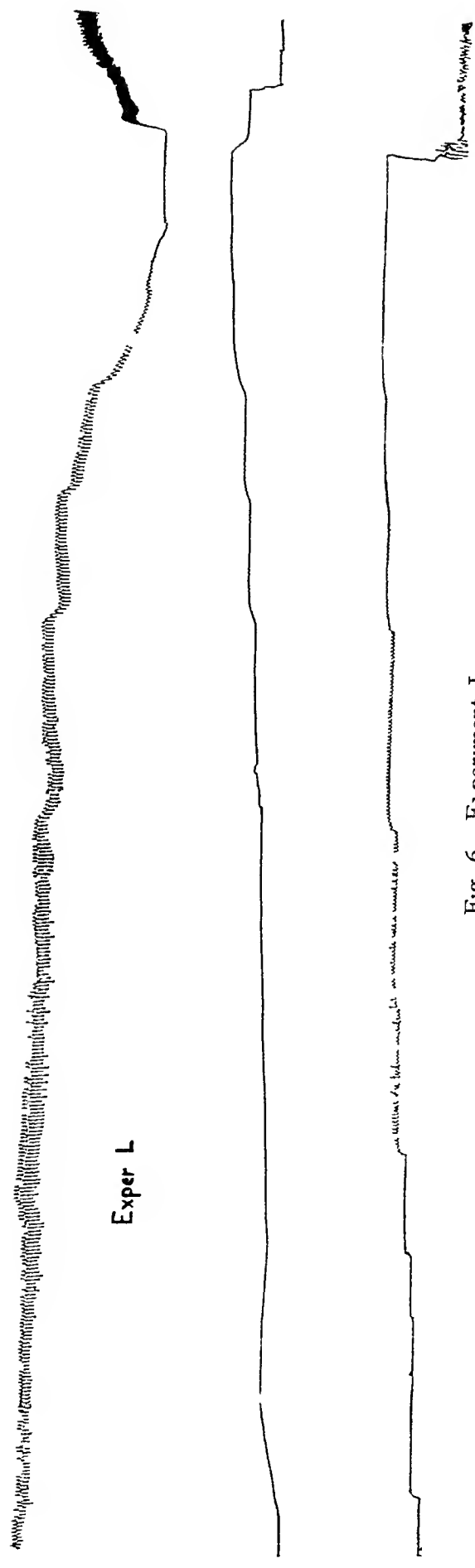


Fig 6—Experiment L

thirteen dogs were used in all, and, as stated, in most cases several tracings taken one after another from the same animal, they were practically identical, so that, to economize space, only a few examples are given. The lowest line on the tracings indicates the intrapericardial, the middle line, the venous, and the top line the arterial pressure.

CONCLUSIONS

1 A not inconsiderable number of patients with substantially uncomplicated pericarditis with effusion die a typical pericardial death, that is, die as the result of the pressure of the exudate shutting off mechanically the great veins.

2 The pressure in the pericardial sac is the real criterion of the danger, and this is not proportional to the size of the exudate, but rather to the rapidity with which the effusion develops.

3 A steady fall in the arterial pressure and particularly a sudden increase in the rate of fall, is a direct indication for therapeutic puncture and relief of the pressure.

THE RELATION OF MONILIA TO INFECTIONS OF THE UPPER AIR PASSAGES *

A J KOTKIS, M D
M WACHOWIAK, M D
AND
MOYER S FLEISHER, M D
ST LOUIS

The occurrence of yeasts or yeastlike organisms in the respiratory tract of normal or sick persons is by no means an unrecognized occurrence. It has long been accepted that fungi (named usually as monilia or endomyces) are agents in the causation of thrush. In recent years reports have appeared in increasing numbers concerning the presence of fungi in affections of the upper air passages of man. It has been shown by a number of observers that fungi can be found in the upper air passages of normal persons, and also, possibly as secondary invaders, in the air passages of persons suffering from infections apparently primarily due to some bacterial agent¹. The presence of fungi, generally of the class of the imperfect fungi, has been demonstrated in a number of cases of bronchitis, such cases have been reported from various parts of the world but principally from the tropics². And, finally, fungi of similar types have been demonstrated in pulmonary lesions³ in which no other specific causative agent was shown to be present.

We are presented then with the facts that fungi imperfecti are to be found in the upper air passages of normal persons and also of persons with the lesions of either the mouth, the bronchi or the lungs. These organisms are to be found in certain conditions of disease and it often appears that their presence serves as the only recognizable factor to explain the causation of the particular disorder. It is difficult, therefore, to determine definitely the relationship of these fungi to disease.

* From the Department of Bacteriology and Hygiene, St. Louis University School of Medicine.

1 Tanner and Dack. *Centralbl f Bakteriöl* **91** 282, 1924. Castellani. *Ann. de l'Inst Pasteur* **30** 149, 1916.

2 Castellani and Chalmers. *Manual of Tropical Medicine*, Philadelphia, William Wood & Company, 1922, pp 1886-1891. Steinfield, E. *J Lab & Clin. Med* **8** 744 (Aug) 1923, *Bronchomycosis Associated with Certain Types of Bronchial Asthma*, *J A M A* **82** 83 (Jan 12) 1924. Sur, T. *Indian M Gaz* **56** 445 (Dec) 1921. Castellani, A., Douglas, M., and Thompson, E. T. *J Trop Med* **28** 257 (July 15) 1925.

3 Sanfilippo, cited in *Rev de med* **42** 104, 1925. *Bullet Medical Paris*, 1921, p 35. Jaumain, D., and Colard, A. *Compt rend Soc de biol* **93** 858 (Sept 30) 1925.

We have had the opportunity to study cultures from a number of patients suffering with infections of the upper air passages, that is, patients with thrush or bronchitis. From some of these we have been able to isolate fungi, and it would appear that these organisms were related to the disease or were a factor in causing the symptoms. We wish to report here briefly concerning the organisms isolated from these patients and to consider the relationship of the organisms isolated to the particular conditions.

In three cases of mouth infection (thrush) we have found monilia or monilia-like organisms, all of which are in general very similar in form and in cultural qualities. Two of these cultures were obtained from babies in whom there existed quite evident buccal lesions and both cases cleared up quite readily under treatment. In one of these cases the organisms were also present in the stool, and there was associated with the lesions in the mouth a diarrhea which stopped as soon as the oral lesions disappeared. The third patient was an adult and the lesions of the mouth were the only evident symptoms, here also the symptoms cleared quite readily. We could not by studying the growth of the organisms on various simple mediums differentiate between the organisms found in the two cases from the infants and the one found in the adult, the three organisms appeared to be identical or at least closely related. At least temporarily we classify these organisms as monilia.

We have also taken cultures from a number of patients with bronchitis associated with asthma, these were, without exception, cases in which the affection had been of rather long duration and in which no evident causative factor had been determined. We have examined the sputum from fourteen such patients but found the fungi present in only five of the cases examined. In all five of those cases in which fungi were shown to be present, we isolated organisms that were similar to those found in the cases of mouth infection, organisms, therefore, which we, for the present at least, must class as monilia.

Two of these patients were treated with vaccines prepared from the organisms isolated from the particular cases and in both an improvement occurred. One of the cases, however, passed out of our control before a full course of treatment could be completed and, therefore, we are unable to state the final result. In the other patient an almost complete disappearance of the symptoms followed the treatment with the vaccine.

As we have stated above, there was a marked similarity, if not complete identity between the organisms isolated from the patients in whom a mouth infection existed and those isolated from patients who suffered from bronchitis. In all cases, the growth on Sabouraud's medium was creamy white, raised and glistening. In pour plate cultures there appeared mycelial outgrowths with masses of conidia at the

junction of the articles. The reactions in carbohydrate mediums were in general similar but not identical, as shown in the accompanying table.

We do not, at the present time, desire to lay too much stress on the differences noted here in the action of the various strains on carbohydrates. It is possible, and from the reactions recorded in the table seems probable, that we are dealing with different species of monilia, however, it seems quite likely that we deal with a number of closely related species. We find that no two cultures show identical actions on the various carbohydrates and we are in doubt as to how we should interpret these differences in connection with classification of these organisms. At the present time, then, we prefer to group these organisms only as monilia.

*Reactions in Carbohydrate Mediums of Organisms Isolated from Patients with Mouth Infection and from Patients with Bronchitis **

Infection of	Culture Number	Milk	Gelatin	Dextrose	Levulose	Galactose	Saccharose	Maltose	Lactose	Inulin	Dextrin
Mouth	117	Alk, Cg	Arb	AG	AG	A	AG	AG	0	A	A
Mouth	118	Alk, Cg	Arb	AG	AG	A	A	AG	0	0	A
Mouth	216	Alk, Cg	Arb	AG	AG	A	A	AG	0	0	AG
Bronchus	150	Alk, Cg	Arb	AG	AG	A	AG	A	0	A	A
Bronchus	166	Alk, Cg	Arb	AG	AG	AG	A	A	0	A	A
Bronchus	215	Alk, Cg	Arb	AG	AG	0	A	A	0	0	AG
Bronchus	220	Alk, Cg	Arb	AG	AG	AG	AG	AG	0	0	A
Bronchus	262	Alk, Cg	Arb	AG	AG	A	AG	AG	0	0	A

* Alk means medium becomes alkaline, Cg, coagulation of casein, Arb, arborescence, A, acid production, G, gas production, and 0, no change.

In no cases were ascospores seen nor morphologic or cultural qualities that would warrant our considering these organisms as belonging to any group other than the fungi imperfecti.

The question that arises in view of these findings and the findings of other investigators is as to the exact relation of these monilia to infections of the upper air passages.

It has been accepted as fact for many years that the causative agent of thrush is a fungus, called by some a monilia, by others oidium and by still others an endomyces. Castellani and Chalmers ⁴ have stated that thrush may be due to a number of different fungi, and they have noted twelve species of monilia, three species of oidia, a hemispora, wilha, endomyces, and possibly some saccharomyces. We should keep in mind that in most cases of thrush the infection is not severe nor does it tend to cause a high mortality, presumably, therefore, we deal with an organism of a low degree of virulence. But the vital point is, on the other hand, that we do accept the fact, and there seems to be ample proof, that these various fungi may be pathogenic agents in the human organism.

4 Castellani and Chalmers (footnote 2, pp 1741-1744)

At the present time we are studying in this laboratory the pathogenicity of these and similar organisms in rabbits. The experiments so far seem to show that the virulence of different strains of monilia is quite variable and that in general large numbers of organisms must be administered to cause the death of the animals. However, it appears that when these organisms are administered intratracheally they practically always cause the death of the animals, which show at necropsy a pneumonia and a generalized infection with the monilia. It appears then that these organisms are variable in their action, that they are, however, relatively avirulent, but that they may have an affinity for the tissues of the respiratory system.

When then we find similar organisms associated with certain cases of bronchitis or asthma, it appears quite reasonable and quite plausible to assume that here also these organisms may be a factor in the continued irritation and inflammation of the deeper air passages. This assumption has, of course, been accepted by many investigators and fungi have been fairly generally accepted as agents in causing bronchitis. Possibly, the relatively satisfactory results obtained by treatment of some of these cases with an autogenous vaccine may also serve to strengthen the acceptance of the relationship of these organisms.

Granting, however, the likelihood and even accepting as a fact that these fungi do cause bronchitis, we should, in our etiologic study, probably go further than simply accepting this relatively avirulent agent as a causative factor.

We know that in thrush the infection occurs usually in infants and most frequently in undernourished persons. Probably in the great majority of cases the individuals affected, either young or adult, are suffering from some condition that we may say lowers their resistance. We recognize this lowered resistance as a factor in the occurrence of infections in the mouth in which these fungi play a rôle. It would, therefore, appear only reasonable that when similar organisms are found associated with bronchitis and are assumed to be the causative agent, we should, reasoning by analogy, expect that the monilia are not alone as the causative factors, but that other factors, possibly of equal importance, also play a rôle.

We might here call attention to the fact that in two cases of rather advanced tuberculosis (two cases not included in our series here) we were able to demonstrate monilia in the sputum. We believe that in these cases the yeastlike organisms were essentially secondary invaders.

It seems reasonable to assume that the monilia are secondary or concomitant factors, although possibly they may be the chief ones in maintaining the chronicity of the symptoms. It is quite possible that some irritant agent, bacterial, toxic or mechanical, may initiate in the mucosa of the bronchus certain changes, as a result of which the monilia

are now able to grow and to maintain their existence here. If these assumptions are correct, we would have to interpret bronchomoniliasis and probably many types of bronchomycosis as conditions in which a primary factor, either still acting or no longer acting, initiated certain changes that permitted the fungi to gain foothold and to find more or less permanent lodgment in the bronchi, that, however, we must consider the monilia or other fungi as the essential and important elements in maintaining the irritation in these locations. In studying such cases, then, we should as a rule look beyond the relatively avirulent monilia, without in any way ignoring the rôle of these fungi, for some other possible factor in the causation of the chronic inflammation.

CORONARY THROMBOSIS WITH CONGENITAL ABSENCE OF THE LEFT CORONARY ARTERY

FRED M SMITH, M D

AND

V C GRABER, M D

IOWA CITY

The clinical features of coronary obstruction are fairly generally known. The character and distribution of the pain associated with definite changes in the cardiac findings constitute a clinical picture that is rarely unrecognized by those familiar with the condition. This case is of particular interest because of the congenital absence of the left coronary artery.

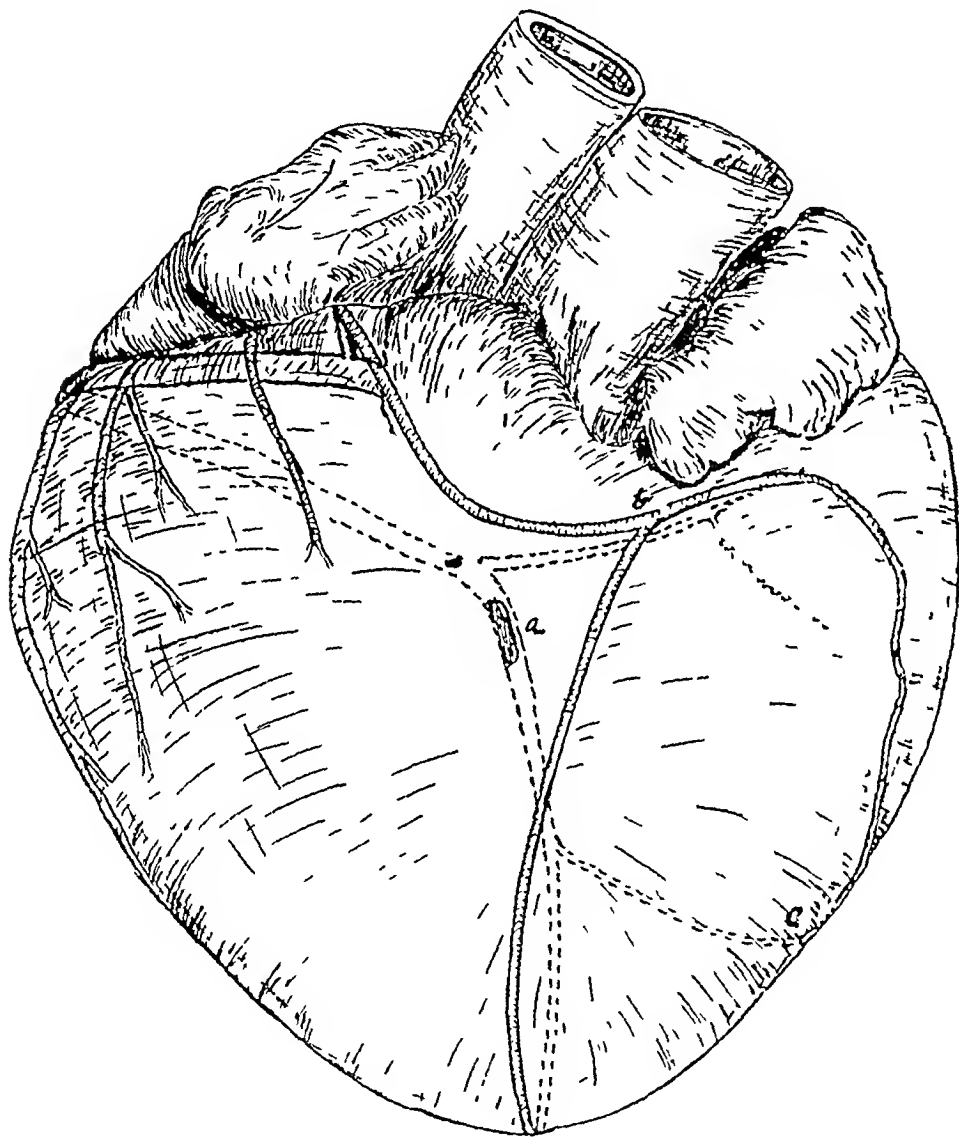
REPORT OF CASE

History—S B, a man, aged 46, was admitted to the University Hospital, May 26, 1925. He complained of severe pain over the lower sternal region and shortness of breath. He stated that he had been working in a stone quarry and was obliged to push cars filled with stone. While pushing a car the day prior to entering the hospital, he was suddenly seized by a severe pain over the lower anterior chest which appeared to be beneath the sternum. The pain was so severe that he was compelled to stop work immediately. He was very short of breath and because of dizziness had to lie down. He was, however, unable to lie flat because of the pain and shortness of breath. The distress continued throughout the day and night and was still severe when he was admitted to the hospital.

The past history was essentially negative except for gonorrhea in 1910 and a nocturia for the last five or six years. He stated that he had not had syphilis. It was later discovered, however, that he had been treated for a syphilitic infection. He was a moderate user of tobacco and alcohol. He was married and had three living children. Five died during infancy.

Physical Examination—The patient was well developed and nourished. He was apparently in great distress and complained of pain over the lower sternal region. He was obliged to sit up because of shortness of breath. The pupils were equal but reacted rather sluggishly to light. The face, nose and ears were negative. The mucous membrane of the mouth was cyanotic but otherwise normal. The pharynx was slightly congested. There were no scars. The neck was negative for glands and the thyroid was not enlarged. The chest was symmetrical and well developed. The expansion was limited because of pain and dyspnea. The percussion note was slightly impaired at the base and moist râles were heard. The apex impulse was not visible, but was palpated slightly outside and below the nipple. The left border of the cardiac dulness extended 3 cm beyond the mid-clavicular line in the fifth interspace. There was no apparent increase in the substernal dulness. The cardiac tones were poorly differentiated and there was a gallop rhythm. The aortic second tone was slightly accentuated. No murmurs were heard. The cardiac rate was 120 per minute and the rhythm was regular. The systolic blood pressure was 90 and the diastolic 68. The pulse volume was small and easily compressed. There was no apparent thickening of the wall of the brachial or radial arteries. The liver was easily palpated and tender. There was no tenderness elsewhere in the abdomen and no tumor masses were felt. The extremities were negative and the reflexes and sensations were intact.

The temperature on admission was 101 F. In the blood count hemoglobin was 85 per cent, red blood cells totaled 4,320,000 and white blood cells 9,000. The urine was negative. An electrocardiogram was taken on the eighth day after admission to the hospital. The amplitude of the Q-R-S group was markedly diminished and the duration increased. The chief ventricular deflection in Lead I was a negative phase. The T-wave was prominent in each lead. In subsequent curves the T deflection became negative and finally returned to the iso-electric phase. There was no further change in the Q-R-S group.



Main surface arteries of the heart: the course of the arteries on the position aspect is represented by interrupted lines, *a*, site of the thrombus, *b* and *c*, location of free anastomosis.

Present Illness—During the first four days in the hospital the pain was continuous except when relieved by morphine. Thereafter, for the following ten days the distress returned on the slightest exertion. A temperature ranging from 99.2 to 101 persisted for two weeks. On the second day a pericardial friction rub was discovered. The gallop rhythm was a constant finding throughout the period of observation. The systolic blood pressure was never above 100 and on several occasions was below 90. By the end of the second week the shortness of breath had subsided and the signs of passive congestion had disappeared. At the end of two months the patient was allowed to be up in a chair and was gradually per-

mitted to walk August 2, he was discharged from the hospital. His condition, however, was not satisfactory. During the night he was again seized by severe pain in the chest and he became very dyspneic. He returned to the hospital the following morning in a critical condition with the findings of cardiac failure. He improved somewhat for a time, but later the course was progressively downward and he died, November 22, from cardiac failure. The clinical diagnosis was coronary obstruction and cardiac failure.

Necropsy—The necropsy findings will be limited to the heart and aorta, the pericardial cavity contained a few centimeters of clear fluid. The pericardium was adherent to the apical region of the heart. The heart was markedly enlarged. The greatest transverse diameter was 17 cm. The heart with the contained blood and the pericardium weighed 930 Gm. The right chambers were more dilated than the left. The thickness of the wall of a large portion of the anterior and lateral aspect of the left ventricle was definitely reduced. Sections of the musculature in this region were largely replaced by fibrous tissue. The endocardium of practically the entire left ventricle was very pale. Both ventricles contained mural thrombi. There was only one coronary artery opening into the aorta (accompanying figure). The artery leading to this opening was unusually large and followed the normal course of the right coronary artery around the auriculoventricular groove posteriorly to the interventricular septum. At this point the artery divided into two branches, the largest of which descended along the interventricular septum and the smaller continued around the auriculoventricular groove to the lateral aspect of the left ventricle. The descending branch was occluded near its origin by a thrombus (*a*). The lateral vessel, after reaching the apex of the heart passed upward along the interventricular septum on the anterior surface to the auriculoventricular groove. Here the vessel joined (*b*) with a fairly large artery coming down over the base of the right ventricle from the first portion of the main coronary artery which continued lateralward over the base of the left ventricle, then downward to the posterior lateral aspect of the left ventricle. At this point (*c*) it anastomosed with a lateral branch of the occluded posterior descending artery. The sclerosis was most extensive in the early portion of the main artery and in some places was calcified. There were no significant changes in the aorta.

COMMENT

In the case herewith reported there were no clinical manifestations of myocardial weakness prior to the cardiac accident. The patient had been doing the heaviest type of physical work without any discomfort whatever. The symptoms typical of coronary thrombosis¹ were the sudden onset of severe substernal pain which lasted for days and was relieved only by the repeated hypodermic administration of morphine, associated with the appearance of the symptoms of cardiac failure, such as marked dyspnea, cyanosis, edema of the lungs and engorgement of the liver, changes in the cardiac findings, such as increase in size, muffled tones, gallop rhythm and later the discovery of a pericardial rub, together with temperature and leukocytosis. The progressive change in the electrocardiogram and the later clinical course further justified the diagnosis.

The anomaly of the coronary circulation was very unusual. The blood supply to the entire heart was furnished by one large artery which,

1 Herrick, J. B. Clinical Features of Sudden Obstruction of the Coronary Arteries, *J. A. M. A.* 59:2015 (Dec 7) 1912, Thrombosis of the Coronary Arteries, *J. A. M. A.* 72:387 (Feb 8) 1919.

during its early course, corresponded in location with that of the right coronary artery. Later branches were given off which reconstructed in a diminutive manner the descending and circumflex branches of the left coronary artery, as shown in the accompanying figure. The differences in the size of these vessels and the usual two main branches of the left coronary artery was striking. The blood supply to the left ventricle was thus apparently much less than in the normal subject. It was difficult to understand how the blood supply to the left ventricle in this instance permitted the individual to perform heavy physical work. It is possible that the blood supply derived directly from the left ventricular cavity might have compensated for the apparent deficiency in the main coronary vessels.²

The anastomosis of the arteries which supplied the left ventricle was an interesting feature. There was a free anastomosis between the two main branches of the posterior descending artery and the branch coming off from the first portion of the main coronary artery which passed lateralward and downward over the basal and lateral aspect of the left ventricle to the posterior surface (*b* and *c*). This extensive anastomosis was undoubtedly a compensatory development following the coronary accident and had reestablished a fairly satisfactory circulation to the infarcted area. Similar compensatory anastomoses³ have previously been described in man⁴ and have been observed experimentally⁵.

It is to be recalled that the sclerosis of the coronary artery was advanced whereas the aorta was regarded as normal. Even though the patient gave a strongly positive Wassermann reaction, the sclerosis corresponded to the senile type. It was considered that perhaps the anomalous coronary circulation was possibly largely responsible for the advanced changes in the vessels. The one vessel from the aorta furnished a pathway for the blood to the entire heart which is ordinarily supplied by two, and in some instances three distinct arteries. This obviously placed an excessive strain on the lone coronary artery.

The area of infarction was confined to the left ventricle and the changes in the electrocardiogram were similar to those produced experimentally by the ligation of branches of the left coronary artery and to those following the occlusion of corresponding arteries in man.⁶

2 Pratt, F. H. The Nutrition of the Heart Through the Vessels of Thebesius and the Coronary Veins, *Am J Physiol* **1** 86, 1898.

3 Cowan and Ritchie. Diseases of the Heart, London, 1922, p. 42.

4 Oberhelman, H. A., and LeCount, E. R. Variations in the Anastomosis of the Coronary Arteries and Their Sequence, *J. A. M. A.* **82** 1321 (April 26) 1924.

5 Smith, F. M. The Action of the Nitrites on the Coronary Circulation, *Arch. Int. Med.* **28** 836 (Dec.) 1921.

6 Smith, F. M. The Ligation of the Coronary Arteries with Electrocardiographic Study, *Arch. Int. Med.* **22** 8 (July) 1918, The Electrocardiographic Changes Following the Occlusion of the Left Coronary Artery, *Arch. Int. Med.* **32** 497 (Oct.) 1923.

MYCOTIC ANEURYSMS

A REPORT OF TWO CASES *

ROSCOE D LEAS, M D

AND

HARVEY S THATCHER, M D

CLEVELAND

The cases in this report are of particular interest because they offer suggestive clinical evidence as to the mechanism of the formation of a mycotic process, and illustrate the probable cause of pain in such a condition. Clinical evidence also suggests that the pathologic process is the same in arteries and veins, and differs only in the end-result.

Mycotic (bacterial) infection of blood vessels may occur as has been discussed by Stengel and Wolferth,¹ as a result of an embolus in the lumen of a vessel, by implantation of infected material on the intima, or through emboli in its vasa vasorum. In favor of the last named mechanism the following cases are offered as suggestive evidence. In both cases there was pain in the region of artery and vein for a period of time before tumefaction appeared. Since it is generally accepted that an embolus in a large blood vessel does not cause pain if there is adequate collateral circulation, it is reasonable to assume that this symptom was probably due to inflammatory reaction in and about the vessel walls. Furthermore, since pain preceded a palpable thrombus in the jugular bulb it is less likely that the process started as the result of a large embolus than that it started with implantation of infected material on the intima, or small emboli in the wall of the vein. This observation leads to the suggestion that the formative mechanism of a mycotic process is identical in artery and vein. The end-result was a patent aneurysm in the artery and thrombosis in the vein due to difference in pressure and rate of flow in arterial and venous systems. Since pain appeared before tumefaction it is unlikely that pressure on surrounding structures was a contributing factor. It is to be noted, furthermore, that the aneurysms and thrombosed veins were situated in regions of lax tissue, where tumor formation would displace rather than compress contiguous structures.

The sequence of events in these cases, namely, pain and then tumefaction, suggests therefore, that the mechanism of the mycotic process

*From the departments of medicine and pathology of Western Reserve University School of Medicine and the Lakeside Hospital

1 Stengel, A, and Wolferth, C C. Mycotic (Bacterial) Aneurysms of Intravascular Origin, Arch Int Med 31 527 (April) 1923

was an inflammatory reaction in and about the vessel wall, due probably to small, infected emboli in the vasa vasorum

The records of the Lakeside Hospital show a total of 198 aneurysms. Of this number only the two reported in this article can definitely be classed as mycotic in origin. Three others are suspected of such origin, but the evidence is not complete.

Since the report of Stengel and Wolfeith cases have been reported as follows:

- Reifenstein ² Two reported, one of gonococcal and one of pneumococcal origin
 Horsley ³ An aneurysm of the axillary artery with a blood culture positive for nonhemolytic streptococcus
 Kolin ⁴ An aneurysm of the superior mesenteric artery
 Terplan ⁵ An aneurysm of the pulmonary artery with a blood culture positive for *Streptococcus viridans*
 Laubry and Bordet ⁶ An aneurysm of the ascending aorta
 Farley and Morris ⁷ An aneurysm of the femoral artery

REPORTS OF CASES

CASE 1—Mycotic aneurysm of the superior mesenteric artery, hemolytic streptococcus septicemia, acute and chronic bacterial endocarditis, mitral insufficiency, acute and chronic myocarditis, infarcts of kidneys, acute meningitis, tertiary syphilis

History—J. L., a man, aged 36, was admitted to the Lakeside Hospital, Nov. 22, 1924, with a complaint of pain in the right side of the chest, headache and malaise, and died, April 15, 1925.

About two weeks prior to admission he experienced malaise and a severe right frontal headache, which later became generalized over the entire head. His throat had been sore for two days, and the right ear had ached for two or three days. He also had pain in the right side of the chest which was intermittent in character and accentuated by inspiration. On the day prior to admission he had a chill and a drenching sweat.

The patient had one attack of gonorrheal urethritis, but said that he had not had syphilis. He also had several attacks of tonsillitis and migratory arthritis.

His prior hospital admissions were as follows:

The first admission was from Nov. 19, 1917, to March 3, 1918. A diagnosis of chronic myocarditis and chronic valvular endocarditis with mitral insufficiency was made. Treatment consisted of sedatives, tincture of digitalis and salicylates. There was considerable, but not satisfactory, improvement.

2 Reifenstein, B. W. Two Cases of Mycotic Aneurysm, Gonococcal and Pneumococcal in Origin, *Am. J. M. Sc.* **168**: 381 (Sept.) 1924.

3 Horsley, J. S., Jr. Aneurysm of Axillary Artery, *J. A. M. A.* **85**: 189 (July 18) 1925.

4 Kolin, L. Aneurysm of Superior Mesenteric Artery, *Arch. f. klin. Chir.* **123**: 684, 1923.

5 Terplan, K. Mycotic Aneurysm of Pulmonary Artery with Endocarditis of Open Ductus Botalli in Case of Chronic Infectious Endocarditis, *Med. Klin.* **20**: 1331 (Sept. 21) 1924.

6 Laubry, C., and Bordet, F. Aneurysm of Ascending Aorta with Secondary Endocarditis, *Bull. et mém. Soc. Méd. d'hop. de Paris* **47**: 179 (Feb. 2) 1923.

7 Farley, D. L., and Norris, G. W. Mycotic Aneurysm of Femoral Artery, *Bull. Ayer Clin. Lab. Pennsylvania Hosp.* **7**: 57, 1922.

The second admission was from Dec 8, 1921, to Jan 29, 1922. On this admission the diagnosis made was hemolytic streptococcus septicemia, broncho-pneumonia, and the same conditions in the heart as before. A blood culture, December 10, was negative in ninety-six hours, but one taken, December 16, was positive in the same length of time for hemolytic streptococcus. Treatment consisted of salicylates and the routine treatment for pneumonia. There was excellent recovery from the pneumonia, and the heart was not found to differ materially from its prior condition.

The third admission was from June 6, 1922, to July 2, 1922. On this occasion a diagnosis of acute rheumatic fever and chronic valvular endocarditis with mitral insufficiency was made. A blood culture, June 10, was negative in seventy-two hours. Salicylates gave relief from the arthritis, but the heart showed increased size and diminished myocardial reserve. There were no signs of extension of the endocarditis.

Physical Examination—The patient was severely ill with a temperature of 39.4 C, pulse 95, and respiratory rate 23. There was tenderness to pressure over the entire right side of the face and head, particularly over the mastoid and frontal sinuses. The ears, sinuses, throat and lungs showed no abnormalities. The eye-grounds also were normal. The heart had slight right and left ventricular enlargement. There was a systolic murmur over the apex and aortic region, and systolic and diastolic murmurs were audible in the third intercostal space to the left of the sternum. The blood pressure was 120 maximum systolic, and 70 minimum diastolic. The pulse was irregular and arrhythmic. These physical findings were indicative of insufficiency of the mitral valve, but further interpretations were doubtful. The right knee and ankle were tender to pressure. All reflexes were hyperactive, except the left Achilles, which was hypoactive. The neck was stiff and there was a bilateral Kernig's sign, but there were no other abnormal neurologic signs.

Laboratory Data—A blood culture, November 25, was positive in seventy-two hours, yielding one colony per cubic centimeter of blood on dextrose, and eight on plain agar. The organisms were gram-negative cocci in pairs and short chains. They were not agglutinated by pneumococcus antiserum. Another culture, December 31, was positive in seventy-two hours also, and yielded eighteen and twenty-two colonies per cubic centimeter of blood, about which there was a slight zone of hemolysis. The organisms were gram-negative cocci in chains and were identified as hemolytic streptococcus. Electrocardiograms were made in December, 1921, January, 1922, June, 1922, December, 1924, and January, 1925. It is remarkable that the first and last of these records showed a curious, rhythmic trigeminy of the whole heart determined by discharge of impulses from three separate supraventricular foci. The remaining records revealed normal cardiac mechanism, frequently interrupted by blocked and unblocked auricular ectopic beats. In spite of these profound intra-auricular disturbances the patient never had auricular fibrillation.

The white blood cell count was 18,200 on admission, but later varied from 10,000 to 11,000. The red blood cell count on admission was 4,480,000 and hemoglobin 80 per cent. Before death they were 3,820,000 and 75 per cent respectively. The urine showed little albumin, no hemoglobin, numerous white blood cells at times, a few red blood cells and hyaline, granular and cell casts occasionally. The spinal fluid contained 111 cells, from 70 to 80 per cent of which were polymorphonuclear leukocytes. Gram-positive cocci were found in the smears, but the cultures were negative and the organism could not be identified. The spinal fluid Wassermann reaction was four plus, but a later one was negative. The blood Wassermann reaction was four plus, but a later one was negative also. Over a period of five days the patient was given 135 cc of antimeningococcic serum intraspinously in doses of from 15 to 30 cc (November 27 to December 1). There was improvement clinically, and the cell count dropped progressively (93, 16, 7 and 1). There was no bacteriologic proof of the meningitis being

meningococcic in type, but response to the antimeningococcic serum was so excellent that this etiologic agent was suspected

Subsequent Course—Fourteen weeks after admission an aneurysm was noted in the region of the superior mesentery artery, about 4 cm in diameter and about 5 cm to the left of, and slightly above the level of the umbilicus. There was a marked thrill and a high pitched bruit immediately over it. With gentle pressure it could be moved laterally across the spine, but not in the longitudinal axis of the body. The patient had complained bitterly of pain in this location for many weeks, but repeated examination did not reveal the aneurysm until the date named.

This sequence of events, namely, a complaint of pain much earlier than the clinical appearance of the aneurysm, is probably significant as to the cause of pain in such a process. It is scarcely conceivable that an aneurysm of this size and in this position, could produce pain by compression of surrounding structures, furthermore, pain was as prominent a symptom before as it was after the tumor mass was of sufficient size to be palpable. Likewise, stretching of the arterial wall would scarcely account for the pain. A mycotic aneurysm may arise from an infected embolus in the lumen of the artery by implantation of infected material on the intima, or as the result of a weakened arterial wall, due to small emboli in the vasa vasorum. Embolism of a large artery does not cause pain if collateral circulation is adequate, and this symptom arises only after the wall of the artery has been invaded by organisms from the infected embolus. However, emboli in the vasa vasorum of an artery, associated with the resultant degenerative change, would rapidly become a painful process. This mechanism is much more reasonable than simply an embolus in the lumen.

December 12, a small, red indurated area appeared in the skin, at the base of the fifth right metacarpal, which disappeared in a few days and was embolic in nature. On the same day there was a complaint of pain in the right supra-clavicular space. There was swelling and tenderness over the external jugular vein which later became frankly thrombosed.

This sequence of events was exactly similar to that described above. In this instance, however, a vein was involved instead of an artery. Pain was the earliest symptom and was indicative of phlebitis and periphlebitis, prior to the formation of the thrombus. A thrombus resulted rather than an aneurysm because of the lower pressure and slower rate of flow in the vein. Petechiae also appeared in the upper aspect of the right anterior triangle of the neck. December 30, there was one petechia on the tongue, and quite a few more had developed on the palmar surfaces of the hands. February 2, following a complaint of pain and tenderness in the left popliteal fossa and an absent pulsation in the anterior tibial artery, an irregular erythematous area, about 6 by 4 cm, appeared on the dorsum of the left foot. This area was exquisitely tender and disappeared in the course of twenty-four hours. This was another embolic phenomenon. March 2, the right small toe became red, swollen and painful but was also hot to touch, so in all probability the condition was arthritic rather than embolic in origin. This conclusion is based on the observation that plugging of an artery by an embolus gives either no change or a reduction of temperature of the parts distal to the obstruction. March 15, petechiae appeared in the conjunctivae, and in the skin over the distal phalanx of the right middle finger.

An attempt was made to combat the septicemia with mercurochrome intravenously. One hundred and sixty cubic centimeters of a 1 per cent solution were given from January 23 to 29 in doses of 30, 25, 25, 40 and 40 cc, or 5-8 mg per kilogram of body weight. There was no appreciable effect on the temperature or general condition of the patient.

Pathologic Examination—An incision 20 cm long was permitted in the abdomen through which the pathologic examination was made. The body was emaciated. There were numerous petechiae beneath the epidermis of the chest, back, palms of the hands and the soft palate and the conjunctivae. Immediately below the incision, slightly above the umbilicus, there was a hard mass in the peritoneal cavity. It was freely movable laterally and upward but not downward.

This mass communicated with the superior mesenteric artery. It was 7.3 cm long, 5 cm wide and 3.5 cm thick. The interior was 6.2 cm long, 2.1 cm wide and 2.1 cm thick. The width of the wall averaged 4 mm. The interior consisted of a thick, laminated clot of blood, adherent to the dilated wall (fig 1). The organs were removed through the incision in the abdominal wall.

The heart weighed 700 Gm. The parietal pericardium was firmly united to the epicardium throughout the entire surface of the auricle and ventricle by firm, fibrous adhesions. The right auricle contained a few white, fibrous plaques immediately above the anterior leaflet of the tricuspid valve. The tricuspid valve measured 11 cm in circumference. The right ventricular wall measured 0.5 cm in thickness. The pulmonary valve was normal and measured 7 cm in circumference. The left atrium was greatly dilated in contrast to the right atrium, which was only slightly larger than normal. The wall of the left auricle was much thicker than normal and contained white, fibrous plaques. Immediately above the posterior leaflet in the region of the auricular appendage, the endocardial surface contained numerous sessile, papilliform vegetations. They were firmly adherent to the endocardial surface and reddish white. The mitral valve was 11.5 cm in circumference. The leaflets were firmly fused at their line of closure. Both were considerably thickened. The greatest thickness was at the line of closure, and here were numerous yellowish white vegetations, the largest being the size of a pea. These vegetations were more marked on the aortic leaflets. The chordae tendinae were thickened and shortened. Small hemorrhages were within the vegetations. The aortic valve was thickened at its base. It was 7 cm in circumference. The suprasigmoid portion of the aorta contained minute patches of light yellow regions in the intima. The coronary arteries were normal. The surfaces made by sectioning the heart muscle contained a few regions of firm, gray, fibrous tissue, with marked congestion of the interstitial vessels interspersed with small hemorrhagic spots.

Anatomic Diagnosis—There were petechiae of the left visceral pleura and congestion of the lungs, bilateral localized fibrous pleuritis, acute vegetative endocarditis, acute myocarditis, hypertrophy of the left auricle, dilatation of the right ventricle, chronic mitral and aortic valvulitis, chronic adhesive pericarditis, chronic passive congestion of the liver, multiple white infarcts and amyloid formation of the spleen, localized perisplenitis, mycotic aneurysm of the superior mesenteric artery, multiple white infarcts of the kidneys, acute glomerulonephritis, emaciation, and petechiae of the chest, back, palms of the hands, soft palate and conjunctivae.

Histologic Diagnosis—There were congestion and edema of the lungs, acute infectious myocarditis, chronic passive congestion, focal abscesses and slight amyloid infiltration in the liver, chronic lymphadenitis, with amyloid formation of the lymph nodes, amyloid formation and white infarct of the spleen, acute splenitis, perisplenitis, amyloid formation of the suprarenals, white infarct in the kidney, acute infectious glomerulonephritis, and amyloid formation in the kidneys.

Bacteriologic Examination—No heart's blood was taken because of the limitation of the incision.

Section Through Aneurysm of Mesenteric Artery—The walls of the artery were greatly changed. The intima was thickened, and there were considerable necrosis and hyalinization. The endothelial lining had broken or disappeared, and there was breaking of the entire structure.

Most of the elastic tissue had been broken, and in the media much of it had disappeared (Weigert's stain). The muscle fibers also were irregular and broken. Much of the media consisted of fibrous tissue. Certain portions near the intima were hyalinized, and took the eosin stain. The adventitia was thick and fibrous as a rule, although it was thicker in certain regions. There was no sclerosis of the walls of the vasa vasorum. There was considerable fat in the adventitia (sudan III stain). There was no thrombosis of the vasa vasorum, but

a few of them had a slight proliferation of endothelial cells into the lumina. No fibrous tissue was about the nerves (Mallory's aniline blue and van Gieson's stains). There were no organisms (bacterial stains).

From the appearance of the wall, healing had occurred, and the process was chronic.

The case may be summarized as one of bacterial endocarditis with hemolytic streptococcus septicemia, in proof of which there was a positive blood culture, evidence of endocardial and myocardial involvement, embolic phenomena and a mycotic aneurysm. The endocarditis persisted in a chronic, or subacute form with exacerbations for a period of eight



Fig 1—Sacculated aneurysm of the superior mesenteric artery with laminated blood clot on the interior and thickened walls.

years. Acute meningitis was diagnosed on the occasion of the patient's last hospitalization, which may have been streptococcal in origin, but seems more plausibly to have been due to the meningococcus because of the clinical reaction to its antiserum. Syphilis was indicated by serologic reactions but nothing was found clinically to confirm it.

The case is reported because of a mycotic aneurysm in the superior mesenteric artery which developed as a part of the cardiovascular disease. It was under close observation for four weeks prior to death during which time it increased in size and gave rise to severe abdominal pain.

The pathologic examination, however, did not confirm the hypothesis based on clinical findings, that the aneurysm was caused by embolism of the vasa vasorum

CASE 2—Mycotic aneurysm of the superior mesenteric artery, streptococcus viridans septicemia, subacute bacterial endocarditis, aortic valvulitis with insufficiency, acute glomerulonephritis, infarct of the spleen

History—J N, a man, aged 25, was admitted to the Lakeside Hospital, April 4, 1925, complaining of severe pain in the left lumbar region, he died, May 20

About two months prior to admission he was forced to go to bed because of pain in the legs. Shortly afterward his ankles became edematous. About two weeks prior to admission he experienced cramplike pain in the abdomen associated with urination, which was also painful. A few days later he had a twenty-four hour period of anuria. Two days before admission he experienced a severe and persistent knifelike pain in the left lumbar region.

The patient was in the United States navy during the Great War. In 1919, following exposure to wet and cold, he developed an acute migratory arthritis which required hospitalization on shore for about two months. He was told of no cardiac disease before or after this illness, and was returned to active duty. Two years before admission he contracted a gonorrheal urethritis which was properly treated. He was married, and his wife had two children and no miscarriages. Although the patient was conscious of no palpitation of the heart, his wife had noted marked pulsations of the carotid artery for a period of at least two years.

Physical Examination—The patient appeared extremely ill with a temperature of 39.2 C, pulse 126, and respiration 27. The facies and general attitude betokened severe pain. He assumed all sorts of grotesque positions in bed during attacks of pain, which was localized in the left lumbar region. There was marked pallor but no cyanosis of the skin. There were no petechiae. The precordial activity was markedly increased, and a large excursion was noted in the carotid arteries. There was left ventricular enlargement with a choc-en-dome over the apex in the fifth intercostal space between the left midclavicular and anterior axillary lines. Systolic and diastolic murmurs were heard best in the second intercostal space to the right of the sternum, but the aortic closure sound could be heard, and a diastolic impact was palpable over the aorta. The pulse was celer in type, and a capillary pulse also was observed. The blood pressure was 168 maximum systolic, and 78 minimum diastolic.

These cardiac circulatory findings indicated an insufficiency and possible stenosis of the aortic valve, however, the aortic closure sound and diastolic impact over the aorta implied less insufficiency than the type of pulse, character of enlargement of the heart and murmur would presuppose.

The splenic edge was firm, tender and palpable 4 cm. below the costal margin. The eye-grounds showed no hemorrhages, but a slight degree of edema of the left disk.

Laboratory Data—The hemoglobin was 55 per cent, and red blood cell count 3,550,000. The same determinations, eleven days later, were 40 per cent and 2,560,000 respectively. The white blood cell count varied from 17,200 to 7,000. April 27 the blood culture gave no growth in forty-eight hours, but in seventy-two hours a plate gave eight colonies per cubic centimeter of blood, which showed gram-negative cocci in chains. There was no hemolysis. A second blood culture, May 1, gave no growth in twenty-four hours, but in forty-eight hours there were seventeen colonies of a gram-positive coccus in chains and diplo formation. There was no reaction with pneumococcus antiserum. Again, May 19 a culture was positive in seventy-two hours giving eleven colonies per cubic centimeter of blood on dextrose, and four on plain agar. The organisms were gram-negative cocci in chains, and were identified as *Streptococcus viridans*. The urine was

dark red and smoky, and contained from 1 to 2 Gm of albumin per liter, hemoglobin, red and white blood cells, and many cellular and granular casts. The blood urea rose from 51 mg per hundred cubic centimeters on admission to 210 mg shortly before death. Blood uric acid was from 3 to 4 mg per hundred cubic centimeters. Roentgen-ray examination of the urinary tract was negative for stones, and the kidneys were not enlarged. The blood Wassermann reaction was negative.

Subsequent Course—Two weeks after admission an aneurysm was noted in the abdomen, which was about 4 cm in diameter and could be moved from its position on the left (just lateral to the umbilicus) about 4 cm to the right, but



Fig 2—Vegetations on aortic leaflets, orifice of small mycotic aneurysm of aorta immediately above left posterior leaflet

not in the longitudinal axis of the body. Pain had been present in this location since admission. The tumor possessed expansile pulsation which could be identified as separated from that of the aorta. At times a thrill was palpable over it, and there was a constant murmur coincident with cardiac systole which could not be heard over either femoral artery.

Petechiae appeared in the mucosa of the mouth and over various parts of the body during the course of the disease. Hemorrhages appeared in the retinae. There was rigidity of the neck and a bilaterally positive Kernig's sign indicating meningitis just prior to death.

Two hundred and twenty-five cubic centimeters of a 1 per cent gentian violet solution was given over a period of ten days, in doses of from 25 to 30 cc (4 to 5 mg per kilogram), with no appreciable effect. A blood culture was positive after administration of the dye.

On the morning of his sudden death the patient complained of severe pain over the precordium, but examination revealed no change of physical signs.

Pathologic Examination—The body was emaciated. The pericardial sac was markedly distended with fluid and clotted blood. There were 400 Gm of clot and 430 Gm of serum. This blood was from a small aneurysm 3 cm in width immediately above the upper edge of the right posterior aortic valve. The aortic valves had numerous vegetations on them. The anterior cusp had a huge vegetation on it 2.1 cm long, 0.8 cm wide and 1 cm thick. It extended on both sides of the leaflets. It was green and red and consisted of numerous small, irregular nodules. The other vegetations were gray and red, and also consisted of numerous small, irregular nodules. They were gray and red.



Fig 3—Aneurysm of superior mesenteric artery with origin and its relations

and were not profuse. Vegetations extended into the ring of the aneurysm from the upper surface of the posterior cusp, and they also extended on the posterior surface of the mitral leaflets (fig 2). The heart weighed 450 Gm. The muscle was dull throughout.

The aneurysm of the superior mesenteric artery began 5.7 cm from its origin. The opening was well defined but the lower portion of the aneurysm extended in several branches of the artery. It was 5 cm long and 3 cm wide. It contained only slightly clotted blood which was easily removed, leaving a clear, gray, smooth surface. The width of the wall was 1 mm (fig 3).

The lining of the aorta contained a few small patches of sclerosis.

Anatomic Diagnosis—There were edema and congestion of the brain, petechiae of the pleura, localized fibrous pleuritis, organizing bronchopneumonia, mycotic aneurysm of the aorta with rupture in the pericardial sac, acute parenchymatous degeneration, 'milk patch' of the pericardium, slight atherosclerosis, sacculated

aneurysm in the superior mesenteric artery, acute splenic tumor, red and white infarcts in the spleen, acute parenchymatous degeneration of the liver lessened yellow material in the cortices of the suprarenals, acute glomerulonephritis, petechiae in the lining of the stomach, slight localized congestion of the urinary bladder, chronic prostatitis, acute emaciation, missing teeth, and scars of the legs

Histologic Diagnosis—There were organizing bronchopneumonia, chronic pleuritis, acute interstitial myocarditis, acute pericarditis, acute periaortitis, red infarct and amyloid formation in the spleen, acute perisplenitis and acute glomerulonephritis

Bacteriologic Examination—No organisms were found in the heart's blood or pericardial fluid

Aneurysm—The intima and half of the media were markedly necrotic and stained red with considerable nuclear debris. The debris contained polymorphonuclear leukocytes. In one section there was a definite abscess in the media. Here the adventitia was thin. Bordering this necrotic region the media was fibrous as well as the adventitia. The endothelial lining had disappeared in several sections. The contour of the internal elastic membrane was destroyed and fragments remained. The elastic tissue was broken in certain regions or had disappeared (Weigert's stain). There was a slight amount of fat in the adventitia (sudan III stain). Compared with the normal aorta bordering the aneurysm, the walls of the aneurysm were thicker. There was no thrombosis of the vasa vasorum, but a few of them contained proliferated endothelium. No fibrous tissue was about the nerves (Mallory's aniline blue and van Gieson's stains). No organisms were found (bacterial stains).

Section of the Aorta—There was marked infiltration with polymorphonuclear leukocytes and pink staining material in the adventitia. The extreme outer surface of the media was involved. This infiltration was especially noticeable about the vasa vasorum.

The process was acute with evidence of healing.

This case may also be summarized as one of bacterial endocarditis with *Streptococcus viridans* septicemia, in proof of which there was a positive blood culture, evidence of endocarditis, embolic phenomena and a mycotic aneurysm.

Historically it would appear that the patient had an attack of rheumatic arthritis five years prior to this hospitalization, at which time he may have developed endocarditis. Whether this attack was an exacerbation of a chronic or subacute endocarditis or a recent and separate process remains a question.

The case is reported because of mycotic aneurysms of the superior mesenteric artery and the aorta. The former developed and progressed in much the same way as in case 1, and the latter ruptured into the pericardial sac. Emboli were not found in the vasa vasorum, but there was an inflammatory reaction about these vessels.

SUMMARY

1. In two cases of mycotic aneurysms each patient had an aneurysm in the superior mesenteric artery, and one in the aorta.

2. One patient also developed a mycotic process (thrombosis) in the jugular bulb.

3 Pain was a prominent symptom before tumefaction appeared, which was suggestive of embolism of the vasa vasorum as the causative factor in both arteries and veins. Pathologic examination, however, did not confirm this clinical hypothesis.

4 In one case the blood culture was positive for hemolytic streptococcus, and in the other for *Streptococcus viridans*.

5 The administration of gentian violet and mercurochrome intravenously did not modify the course of the disease.

GASTRIC ULCER

IV EXPERIMENTAL PRODUCTION OF GASTRIC ULCER BY LOCAL ANAPHYLAXIS *

PHILLIP F SHAPIRO, M S

AND

A C IVY, PH D, M D

CHICAGO

The literature has been saturated with extensive reviews on the etiology and on the experimental production of gastric ulcer¹ But a painstaking search failed to reveal any work on, or even a direct suggestion of the possibility of, local anaphylaxis as a spontaneous or experimental cause of this lesion² The whole field of local anaphylaxis has attracted but little attention, and almost all the work has been done on the skin

The pioneer work on cutaneous local anaphylaxis was done in 1903 by Arthus³ The phenomenon observed by him was given his name He reported that if rabbits were injected subcutaneously with a foreign protein at five day intervals the local toxicity of the protein steadily increased Thus, the first three injections were absorbed rapidly The fourth induced a soft infiltration which lasted from two to three days The fifth produced a hard infiltration which remained for five or six days At the site of the sixth injection, a solid, white caseous mass developed At the seventh, superficial necrosis terminated in a cuta-

* From the Hull Physiological Laboratory of the University of Chicago and the Department of Physiology and Pharmacology of Northwestern University Medical School

1 Stewart, M J Etiology of Peptic Ulcer, Brit M J **2** 955-958 (Nov 24) 1923 Rosenow, E C Causation of Gastric and Duodenal Ulcer by Streptococci, J Infect Dis **19** 333 (Sept) 1916 Aschoff, L Relations of Mucosal Erosions to the Development of Ulcer of the Stomach, Lectures on Pathology, New York, 1924, p 279 Ivy, A C Studies on Gastric and Duodenal Ulcer, J A M A **75** 1540-1542 (Dec 4) 1920 Palier, E Etiology of Gastroduodenal Ulcer, Why the Stomach Does Not Digest Itself, New York M J **117** 659-662 (June 6) 1923 Ivy, A C Studies on Gastric Ulcer, Arch Int Med **25** 6 (Jan) 1920 Turck, F B Experimental Studies on Round Ulcer of the Stomach and Duodenum, Illinois M J **6** 631-634, 684 (June) 1908 Durante, L Trophic Element in Origin of Gastric Ulcer, Surg Gynec Obst **22** 399 (April) 1916 Bolton, C Ulcer of the Stomach, London, 1913 Rosenow, E C Production of Ulcer of the Stomach by Injection of Streptococci, J A M A **61** 1947 (Nov 29) 1913 Karsner, H T The Pathology of Peptic Ulcer of the Stomach, J A M A **85** 1376 (Oct 31) 1925

2 Hayashi, T Experimentelle Beitrage zur Frage der Ulcurentstehung, Ztschr f d ges exper Med **34** 224-278, 1923

3 Arthus, M, and Breton, M Cutaneous Lesions Produced by the Injection of Horse Serum in a Rabbit Sensitized to This Serum, Compt rend Soc de biol, 1903, p 1478

neous ulcer which healed only after several weeks. He further established the fact that the reaction was not a result of the protein injection per se, for only 0.5 cc of the solution would suffice to give a huge reaction area, and would give a reaction only in specifically sensitized animals. Nonspecific protein injections were without effect. The preliminary sensitization could be effected by any parenteral route. The severity of the local reaction differed with the tissue in which it took place. The skin of the ear, for example, was found to be far less susceptible to local anaphylaxis than was the abdominal wall.⁴



Fig 1—Pyloric mucosa of rabbit sensitized to beef protein, precipitin titer of 256,000, three days after local injection, ulcer was 18 by 12 mm

Nicolle in 1907 established the anaphylactic nature of this local reaction by demonstrating that it could be elicited in an animal sensitized passively.⁵ This showed that local anaphylaxis depended on specific substances transmissible in the serum.

Opie exhaustively elaborated this work in the light of modern conceptions of anaphylaxis.⁶ He made additional contributions to the

4 Arthus, M. Repeated Injections of Horse Serum in a Rabbit, *Compt rend Soc de biol*, 1903 p 817

5 Nicolle, M. Contributions to the Study of the Arthus Phenomenon, *Ann de l'Inst Pasteur* **21** 128, 1907

6 Opie, E. L. Inflammatory Reaction of the Immune Animal to Antigen and Its Relation to Antibodies, *J Immunol* **9** 231-245 (July 24) 1924, Relation of Local "Sensitization" to Immunity, *ibid* **9** 259-268 (July 24) 1924, Fate of Antigen in an Animal Immunized Against It, *J Exper Med* **39** 659, 1924, Relation of Antigen to Antibody in Arthus Phenomenon, *J Immunol* **9** 255-257 (July) 1924

effect that (1) cutaneous local anaphylaxis was not produced with equal readiness in all species, (2) the severity of the Arthus phenomenon varied directly with the precipitin titer, but that there was not an exact parallel, (3) the reaction depended on the simultaneous presence of antigen and antibody in the tissue, (4) a period of desensitization followed the response to a pure antigen but not to a complex one, and (5) the local reaction protected the animal from a general reaction by limiting the antigen to the site of injection. He gave gross and microscopic descriptions of the pathologic changes that occurred. Significant in relation to our work was his statement that tissues of the internal organs might react to the antigen as did skin. He found that injection

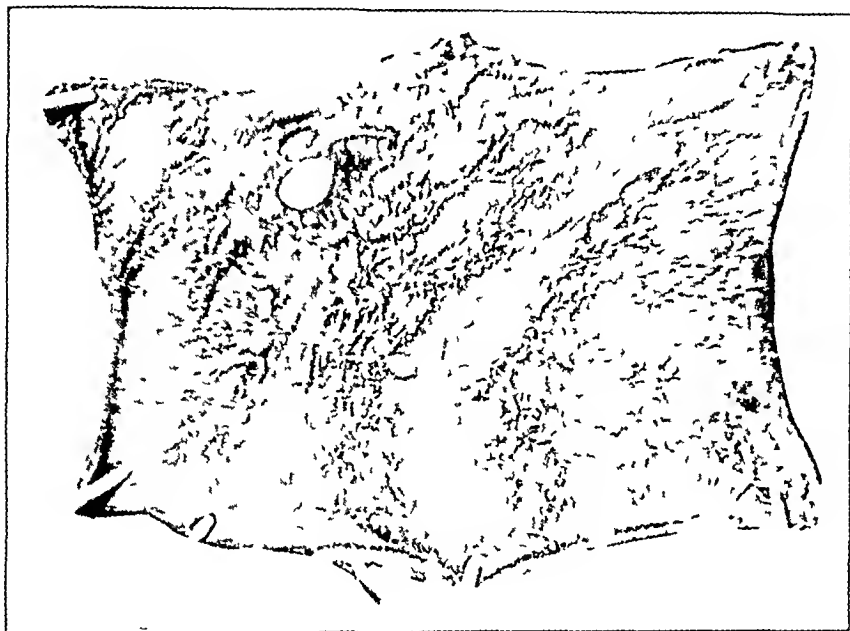


Fig 2—Perforated ulcer at pylorus of rabbit sensitized to edestin, precipitin titer of 256,000, the animal died four days after gastric injection and the stomach was examined while the body was still warm

of specific antigen into the lungs of sensitized animals resulted in a local consolidation

Auer reported that it was not necessary to inject the specific protein locally in order to obtain a local anaphylactic reaction.⁷ If the specific antigen was present in subminimal amounts in the general circulation (intraperitoneal injection) of sensitized animals, a nonspecific irritant could concentrate antigen locally in sufficient amounts to elicit a local gangrene. "A subminimal concentration of antigen for noninflamed sensitized cells became effective for inflamed sensitized cells."

7 Auer, J. Local Auto-Inoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, *J Exper Med* 32:427 (Oct) 1920

TABLE 1—Egg Albumin as Antigen in Rabbits

Ex- peri- ment	Sensi- tizing Protein	Skin Reaction		Specific Precipitin Titer	Stomach Injected with	Interval	Findings at Sites of Injection
		Control	Specific				
1*	Egg al- bumin	Ringer's solution —	Egg albumin +++++	256,000†	Egg al- bumin	1 hour	Marked congestion and edema
2	Egg al- bumin	Ringer's solution —	Egg albumin ++++	256,000	Egg al- bumin	12 hours	Marked congestion
3	Egg al- bumin	Horse serum —	Egg albumin ++++	128,000	Egg al- bumin	24 hours	Congestion with cen- tral necrosis
4	Egg al- bumin	Horse serum —	Egg albumin ++++	128,000	Egg al- bumin	48 hours	Necrosis
5	Egg al- bumin	N/125 sodium hydroxide	Egg albumin ++++	128,000	Egg al- bumin	72 hours	Ulcer, 2 by 2 mm, at pylorus, and 2 by 3 mm at fundus
6	Egg al- bumin	N/125 sodium hydroxide	Egg albumin ++++	128,000	Egg al- bumin	4 days	Ulcer, 3 by 1 mm, at pylorus, and 2 by 3 mm at fundus
7	Egg al- bumin	N/60 sodium hydroxide —	Egg albumin ++++	128,000	Egg al- bumin	6 days	Ulcer at pylorus, 4 by 5 mm at fundus, 2 by 1 mm, surrounded by a papilloma- tous ring
8	Egg al- bumin	Beef —	Egg albumin ++++	128,000	Egg al- bumin	9 days	Ulcer at pylorus, 4 by 5 mm, at fun- dus, 4 by 4 mm
9	Egg al- bumin	Squash —	Egg albumin ++++	128,000	Egg al- bumin	14 days	Large papilloma at pylorus small scar at fundus, incision healed
10	Egg al- bumin	Edestin —	Egg albumin ++++	256,000	Egg al- bumin	39 days	Ulcer at pylorus, 3 by 1 mm, sur- rounded by papil- lomatous ring, papilloma at pos- terior pylorus, scar at fundus incision healed
11	Egg al- bumin	Oats —	Egg albumin ++++	256,000	Egg al- bumin	60 days	Scar at pylorus, nothing in fundus, incision healed
Controls							
12	Egg al- bumin	Squash —	Egg albumin ++++	128,000	Beef	1 day	Small area of slight congestion
13	Egg al- bumin	Edestin —	Egg albumin ++++	128,000	Edestin	4 days	Nothing
14	Egg al- bumin	Oats —	Egg albumin ++++	256,000	Oats	3 days	Nothing
15	None	—	Egg albumin —	0	Egg al- bumin	1 day	Nothing
16	None	—	Egg albumin —	0	Egg al- bumin	5 days	Nothing
Passive Transfers							
17	Passively sensitized to egg albumin	—	Egg albumin +++	16,000	Egg al- bumin	1 day	Marked congestion
18	Passively sensitized to egg albumin	—	Egg albumin +++	16,000	Egg al- bumin	5 days	Firm induration centrally necrotic ulcer at abdominal incision line
19	Passively sensitized to egg albumin	—	Egg albumin +++	32,000	Egg al- bumin	4 days	Ulcer, 3 by 3 mm, at pylorus large area of congestion at fundus

† We represent by one plus slight edema for twenty four hours by two plus, greater edema which lasts for five days, but then disappears, by three plus, hard fibrotic induration which lasts for a much longer time by four plus, necrosis with ulceration

‡ Nonspecific precipitin titers were all negative

* Almost all the experiments were done at least in duplicate, but a typical result only is given in the table as the results in each experiment were practically identical

An anaphylactic reaction could thus, under proper conditions, be caused by substances that did not of themselves produce anaphylaxis,⁸ such as trauma, acid, heat

TABLE 2—*Beef Protein as Antigen in Rabbits*

Experiment	Skin Reaction		Specific Precipitin Titer	Stomach Injected with	Interval	Observations at Sites of Injection
	Control	Specific				
20	Oats	Beef +++	32,000	Beef	1 hour	Congestion and edema
21	Egg albumin	Beef ++++	128,000	Beef	16 hours	Congestion and edema
22	Horse serum	Beef +++	32,000	Beef	48 hours	Firm infiltration, 6 by 9 mm
23	Horse serum	Beef ++++	128,000	Beef	60 hours	Ulcer, 3 by 1 mm, at pylorus
24	Squash	Beef ++++	256,000	Beef	72 hours	Ulcer, 8 by 10 mm
25	Squash	Beef ++++	128,000	Beef	4 days	Ulcer, 6 by 8 mm
26	Squash	Beef ++++	128,000	Beef	5 days	Ulcer, 5 by 1 mm
27	Edestin	Beef ++++	128,000	Beef	9 days	Ulcer, 5 by 3 mm
28	Edestin	Beef ++++	256,000	Beef	15 days	Small scar at pylorus
29	Controls Egg albumin	Beef ++++	256,000	Egg albumin	5 days	Nothing
30	Not sensitized		0	Beef	3 days	Nothing
31	Passively sensitized to beef		32,000	Beef	2 days	Ulcer at pylorus, 3 by 3 mm, large area of congestion at fundus

TABLE 3—*Edestin as Antigen in Rabbits*

Experiment	Skin Reaction		Specific Precipitin Titer	Stomach Injected with	Interval	Findings at Sites of Injection
	Control	Specific				
32	Squash	Edestin ++++	16,000	Edestin	12 hours	Congestion
33	Egg albumin	Edestin +++	16,000	Edestin	1 day	Congestion with central necrosis
34	Egg albumin	Edestin ++++	128,000	Edestin	36 hours	Congestion with central necrosis
35	Horse serum	Edestin ++++	128,000	Edestin	4 days	Perforated ulcer, 3 by 2 mm, large area of congestion
36	Horse serum	Edestin ++++	64,000	Edestin	6 days	Nodule at fundus ulcer at pylorus, 2 by 2 mm
37	Oats	Edestin ++++	32,000	Edestin	17 days	Hard mass at pylorus, 2 by 1.5 cm, nothing at fundus—ulcer of incision healed
38	N/60 sodium hydroxide	Edestin ++++	32,000	Edestin	47 days	Nothing in stomach, incision healed
39	Controls N/60 sodium hydroxide	Edestin ++++	32,000	Beef	2 days	Nothing
40	Not sensitized		0	Edestin	2 days	Nothing

Grineff has described a therapy of local anaphylaxis.⁹ He found that intravenous injection of small quantities of a foreign protein prevented the subcutaneous reaction to a local injection on the next day

⁸ Wells, H. G. Present Status of Problems of Anaphylaxis, *Physiol Rev* 1 44-80 (Jan.) 1921

⁹ Grineff, D. L'Anaphylaxie locale est-elle justiciable du procede des petites doses de Besredka, *Compt rend Soc de biol* 72 974, 1912

We repeated and confirmed some of Arthus' and Opie's work, and then applied the principle of local anaphylaxis in an attempt at experimental production of gastric ulcer.

METHODS

Since any complete foreign protein molecule soluble in body fluids could serve as an antigen unless racemized by alkalis,¹⁰ we had a wide choice of materials. Ten protein preparations were used: (1) commercial

TABLE 4—Other Proteins as Antigens in Rabbits

Experiment	Sensitizing Protein	Skin Reaction		Specific Precipitin Titer	Stomach Injected with	Interval	Findings at Sites of Injection
		Control	Specific				
41	Horse serum	Beef —	Horse serum + + + +	25,600	Horse serum	4 days	Congestion and induration
42	Horse serum	Egg albumin	Horse serum + + + +	25,600	Horse serum	6 days	Ulcer, 3 by 2 mm
43	Horse serum	Egg albumin	Horse serum + + + +	25,600	Horse serum	8 days	Ulcer in anterior pylorus, 3 by 2 mm, surrounded by papillomatous ring, papilloma in posterior pylorus
44	Horse serum	Egg albumin	Horse serum + + + +	25,600	Horse serum	22 days	Scar in pylorus, nothing in fundus; incision healed
45	Squash	Beef —	Squash + + + +	256,000	Squash	1 hour	Congestion and edema
46	Squash	Beef —	Squash + + + +	256,000	Squash	24 hours	Congestion with central necrosis
47	Squash	Edestin —	Squash + + + +	256,000	Squash	36 hours	Edema in pylorus; congestion in fundus
48	Squash	Oats —	Squash + + + +	256,000	Squash	3 days	Large hard mass in pylorus with central necrosis
49	Oat protein	Egg albumin	Oats + + + +	16,000	Oats	2 days	Large area of congestion
50	Oat protein	Egg albumin	Oats + + + +	64,000	Oats	3 days	Ulcer, 3 by 1 mm
51	Oat protein	Squash —	Oats + + + +	16,000	Oats	6 days	Necrotic mass, 11 by 9 mm
52	Oat protein	Squash —	Oats + + + +	16,000	Oats	17 days	Nothing
53	Hemoglobin	Horse serum —	Hemoglobin + + + +		Hemoglobin	1 day	Congestion
54	Hemoglobin	Horse serum —	Hemoglobin + + + +		Hemoglobin	4 days	Ulcer, 2 by 2 mm
55	Hemoglobin	Squash —	Hemoglobin + + + +		Hemoglobin	33 days	Ulcer at fundus 2 by 3 mm; induration at pylorus 2 by 2 mm; incision healed

* Four rabbits sensitized to milk and seven to casein gave negative results; three rabbits inoculated with tubercle bacilli and injected intragastrically with tuberculin gave negative results.

egg albumin (Merck & Co.), (2) commercial beef protein (Wilson & Co.), (3) commercial horse serum (Eli Lilly & Co.), (4) commercial casein (E. H. Sargent & Co.), (5) commercial hemoglobin (Merck & Co.), (6) commercial tuberculin old (Parke, Davis & Co.), (7) milk, (8) squash seed globulin, (9) hemp seed edestin, and (10) oat protein.

¹⁰ Wells, H. G. Chemical Aspects of Immunity, Am. Chem. Soc. Monograph Series, Chemical Catalog Company, 1925, p. 52.

SHAPIRO-HYGIENIC ULCER

Squash seed globulin and edestin were prepared largely after the method described by Abderhalden¹¹. The seeds were ground in a mill. The fat was removed by extraction with ligroine. The fat free crushed seeds were then extracted with 4 volumes of 10 per cent sodium chloride solution. To the filtrate, 4 volumes of distilled water previously heated to 65 C was added. The mixture was slowly cooled to 5 C. The crystalline globulin that separated out on cooling was washed thoroughly with distilled water until salt free, and dried on a Buchner funnel without the use of alcohol-ether.

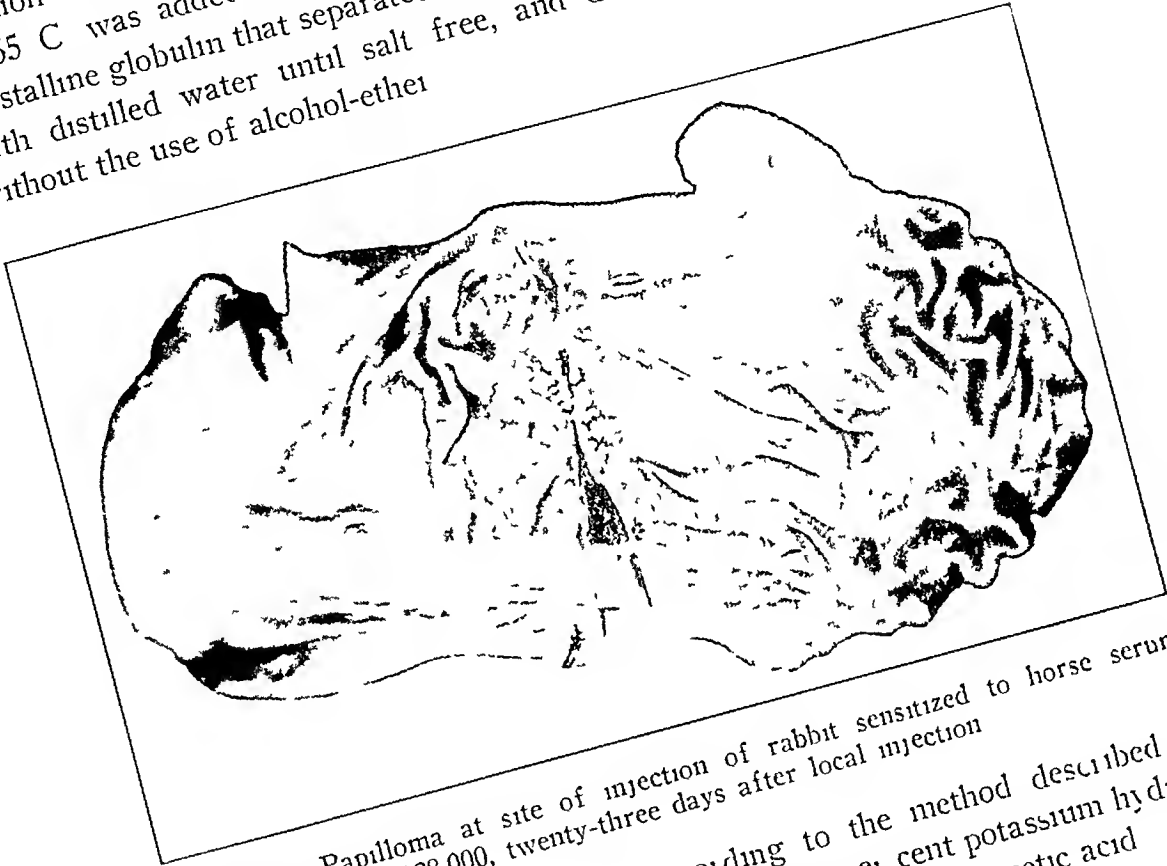


Fig 3—Papilloma at site of injection of rabbit sensitized to horse serum, precipitin titer of 128,000, twenty-three days after local injection

Oat protein was prepared according to the method described by Wells¹². Ground oats were extracted with 1 per cent potassium hydroxide solution and the filtrate therefrom neutralized with acetic acid. This gave a precipitate, which was washed and dried.

The egg albumin, beef protein and hemoglobin were injected in Ringer's solution. The horse serum, milk and tuberculin were used as such. Casein was dissolved to the extent of 4 per cent in 0.2 per cent sodium carbonate, then diluted with an equal volume of distilled water. This gave a 2 per cent solution of casein in 0.1 per cent sodium carbonate solution which was neutralized to clouding by tenth normal hydrochloric acid. Edestin and squash globulin were dissolved in tenth

¹¹ Abderhalden
1910

¹² Wells, H. G., and Osborne, T. B.
Proteins, J. Infect. Dis. 8: 66-24 (Jan.) 1911

Handbuch der Biochem. Arbeitsmethoden, Berlin, 2: 296,
Biological Reactions of the Vegetable

normal sodium hydroxide solution, diluted five times and neutralized as much as possible. All solutions were made up fresh for every injection.

Pyloric pouches were made in ten dogs according to the method described by one of us¹³. The operation consisted essentially of a resection of the pyloric antrum with a gastroduodenal end-to-side anastomosis. The distal end of the antrum was closed. The open proximal end was sewed into an abdominal wall stab wound so that it opened to the exterior. The Heidenhain fundic pouch also was made. It had already been determined that the simple exposure of the mucosa of the pylorus to the exterior for ten months gave no lesion.

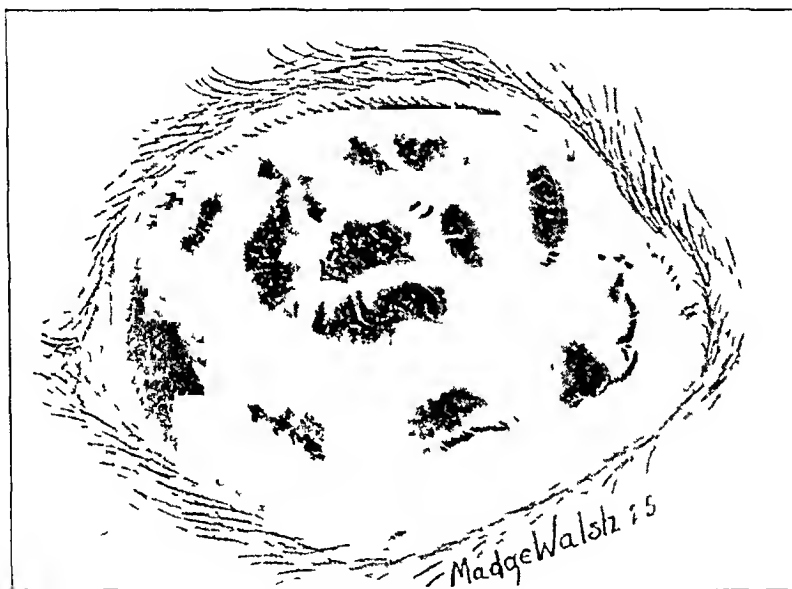


Fig 4—Ulcer in pyloric pouch of dog at site of local injection of egg albumin five days before.

In sensitizing rabbits, we resorted at first to Arthus's original method. Two cubic centimeters of the protein solution was injected subcutaneously at five day intervals until a cutaneous ulcer was obtained. Intravenous or intraperitoneal sensitization at different time intervals with different amounts of antigen yielded the same results. Five days after the last subcutaneous injection, the rabbits were placed under light ether anesthesia. By means of a right rectus incision under aseptic conditions, the stomach was exposed. Five-tenths cubic centimeter of the provocative or control dose was then injected through the serosa and the muscularis into the submucosa of the anterior pylorus and anterior fundus. The period of exposure of the stomach was in no case greater

¹³ Ivy, A. C. Physiology of Stomach Studies on Gastric Ulcer, *Arch Int Med* 25:6 (Jan) 1920.

than three minutes and was usually much shorter. Sensitized and non-sensitized rabbits were injected with nonspecific proteins and with the mediums of injection for controls. The incision was sewed up and, at varying intervals after injection, the rabbits were killed and their stomachs examined.

The dogs were usually sensitized by intravenous injection of the protein, but the subcutaneous or intraperitoneal routes gave similar results. Three 5 cc doses (from 100 to 150 mg each) were injected on successive days. After from twenty to thirty days, 0.5 cc of the provocative or control dose was injected into the submucosa of the



Fig. 5—Ulcer in pyloric pouch of dog at site of local provocative injection of edestin, five days before.

pyloric pouch and into the adjacent skin. Healing time of the ulcers which developed was noted. At varying intervals, the pouch was reinjected. The lesions themselves were then reinjected in an effort to induce chronicity.

To apply Auer's observations to our problem, we reinjected sublethal doses of specific and control antigens intraperitoneally in sensitized dogs. After from thirty to forty-five minutes, a drop of xylene was rubbed on the pyloric mucosa and the reaction observed. The xylene was also applied as a control before reinjection.

To study the effect of gastric motility and acidity on the course of the lesions we placed dogs not previously operated on but sensitized

under morphine-ether anesthesia and aseptically exposed the stomach. The gastric mucosa was exposed by an incision through the anterior gastric wall at the fundus and pylorus. Seventy-five hundredths cubic centimeters of the 2 per cent specific or control solution was then injected into the submucosa of the posterior wall. After different intervals, the dogs were killed and their stomachs examined.

The precipitin titer of the blood was followed in both rabbits and dogs, but satisfactory precipitin changes could be demonstrated only in the rabbits. The titers were run to progressive dilution of antigen by the ring method, in tubes standing for one hour at 37 C.



Fig. 6—Ulcer at site of injection of mucosa of pyloric pouch of dog three days after local injection with beef protein

Rabbits and guinea-pigs were inoculated with tubercle bacilli (HR). After three weeks they were given an intracutaneous tuberculin test. After seven days all positives were injected aseptically in the gastric mucosa with old tuberculin.

Passive immunization was effected in rabbits and attempted in dogs. From thirty-six to forty-eight hours after the transfer, the specific antigen was injected into the gastric mucosa of the recipient.

RESULTS

Our preliminary brief repetition of Opie's work on the production of local skin lesions was so corroboratory that a detailed account of these results would be merely a recapitulation of his. All the protein

preparations used, except casein, milk and tuberculin, gave positive results. With only an occasional exception all the animals used gave identical results, and these were characteristic of the species and of the tissue in which the reaction took place. Control injections with non-specific proteins and with the mediums of solution were, with two exceptions, negative.

Summary of Results in Rabbits—At the site of injection of the specific protein in the gastric mucosa of sensitized rabbits, there developed an orderly sequence of pathologic changes. For from one to two days there was an extensive area of local passive hyperemia and edema. As this slowly disappeared, the central portion of the area became indurated and necrotic. In from three to six days this area indurated sharply, cleanly and regularly. The margins of the ulcer gradually became thicker, often with mucosal proliferation, and rolled in over the base. Healing was usually complete by twelve days. Rarely did an

TABLE 5—*Experiments in Guinea-Pigs*

Experiment	Inoculated with	Interval	Tuberculin Skin Test	Stomach Injected with	Interval	Findings
1	Tubercle bacilli	21 days	+	Tuberculin	1 day	Slight congestion
2	Tubercle bacilli	21 days	+	Tuberculin	3 days	Nothing
3	Tubercle bacilli	21 days	+	Tuberculin	7 days	Nothing
4	Tubercle bacilli	21 days	+	Tuberculin	8 days	Nothing
5	Tubercle bacilli	21 days	+	Tuberculin	9 days	Nothing
6, 7, 8, 9, 10, 11	Tubercle bacilli	21 days	+	Tuberculin	12 days	Nothing

ulcer remain unhealed much longer. The fundic lesions were practically identical with the pyloric.

Casein and milk gave only a slight congestion and edema which entirely disappeared within five days, or left in its wake only a small firm nodule. The tuberculin injection of the gastric mucosa of tuberculous rabbits and guinea-pigs yielded uniformly negative results. The material was rapidly and uneventfully absorbed (table 5).

Rabbits passively sensitized gave results quite similar to those actively sensitized. In all cases the severity of the cutaneous and gastric reactions varied directly but not exactly with the precipitin titer.

Differences in Tissue Susceptibility in Rabbits and in Dogs—A significant feature of our results in the rabbit was the difference in severity of response which various tissues of the same animal displayed to the same antigen injected at the same time and precipitin titer. We had repeated Long's work on the testis by injecting the specific protein directly into that organ of a sensitized animal. Whereas the skin over the testis became necrotic and ulcerated, the underlying organ which had received the blunt of the injection was quite unaffected. The opposite testis which had been injected with a nonspecific protein and

the skin over it were entirely unchanged. We found further in rabbits that the gastric reaction was always slightly less severe than the cutaneous. In dogs we found exactly the reverse conditions. The canine skin persisted in giving as a local anaphylactic reaction nothing more than a transient edema. The gastric mucosa injected at the same time with the same dose of antigen gave an intense four plus reaction with necrosis and ulceration.

Summary of Results in Pyloric Pouch Dogs—Since the reaction in the mucosa could be observed in pyloric pouch dogs ad libitum, the pathologic changes can be more accurately described. Within two minutes after injection of the provocative dose, the pouch contracted violently and everted. The mucosa became blanched, then cyanotic and



Fig 7—Ulcer at pylorus of dog seventeen days after pyloric injection with edestin

markedly edematous. These last changes were most severe at the area of injection. The dog vomited slightly at the first provocative injection. The next day the pouch as a whole had recovered, but at the site of injection there was a large, bluish black, dried area definitely delimited by a narrow red line of active hyperemia. On the third day the central portion of the area turned grayish yellow. By the sixth day the necrotic mucosa had sloughed out leaving a punched out ulcer with a granulating base. The depth of the lesion varied greatly. The edges and base of the ulcer became firm. The ulcer deepened as the edges increased in thickness and began to roll in toward the base. The base was covered later with a glistening, fragile membrane. The overhanging edges gradually approximated over the much broader base, finally fused and became bound firmly down, leaving a scar. Healing time ranged from twenty-one to thirty days.

The reaction to casein and milk stopped at the stage of cyanosis and edema. The mucosa returned to normal within three days. Injection of the various mediums of solution resulted in no change whatever. Injection of nonspecific proteins yielded no reaction at all, or at most a slight edema and congestion which disappeared within an hour. One small ulcer obtained from a nonspecific protein in a cachectic dog healed rapidly. Further reinjection of the same nonspecific antigen into the same and into other animals produced no reaction whatever. Why it occurred, we cannot explain.

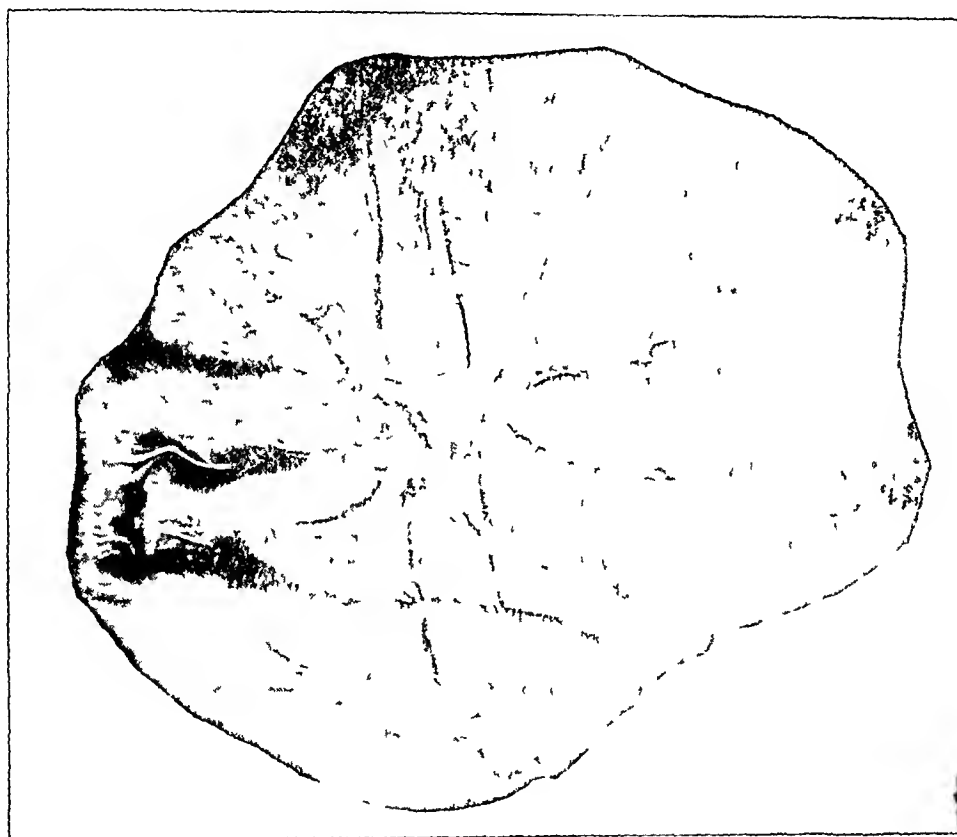


Fig 8—Ulcer at site of fundic injection in the same dog as used in figure 7, lines indicate piece removed for microscopic section

Results Following Repeated Provocative Injections at Various Time Intervals—If the pouch was reinjected with the specific protein at any time within three days after the first provocative injection, there was no reaction. The skin reaction during this period was also negative or slight. A second injection after three days usually yielded a more or less severe reaction, but after four days always another ulcer. This could be repeated until the pouch was fairly riddled with ulcers.

If the reinjections were made in the base or edge of the ulcers, they extended and became terraced. But these four day reactions became progressively less severe than the preceding ones and healed more

rapidly, so that the total healing time of the original ulcer was not appreciably prolonged. After about five reinjections of the pouch at four day intervals, no reaction at all could be elicited. If this refractory pouch was unmolested for about twelve days, reinjection then yielded another ulcer. If a month or more elapsed between pouch injections, there was no response at all, but hypersensitiveness could be built up again by general or local injections.

In two dogs, a second injection after ten days yielded only a local transient cyanosis but a very severe general reaction. The animals collapsed, went into an extensor spasm, defecated, urinated and vomited,

TABLE 6—*First Injection in Dogs*

Dog	Specific Protein	Interval	Control Injection		Control Injection		Specific Injection		Healing Time
			Skin	Pylorus	Skin	Pylorus	Skin	Pylorus	
1	Casein	18 days	0.1% NaCO ₃	—	—	Fdestin	+	Casein Local cyanosis edema and discoloration	2 days
2	Oats	20 days	1/60 sodium hydrosulfide	—	—	Beef	+	Oats Ulcer, 6 by 8 mm slight general reaction (vomiting)	23 days
3	Milk	28 days	Squash	—	—	Beef	+	Milk Slight local cyanosis and edema	1 day
4	Egg albumin	28 days	Ringer's solution	—	—	Squash	+	Egg albumin Ulcer, 1.8 by 1.8 mm, no general reaction	30 days
5	Edestin	29 days	Squash	—	—	Beef	+	Edestin Ulcer, 1.9 by 1.7 mm, no general reaction	30 days
6	Beef	22 days	Edestin	—	—	Egg albumin	+	Beef Ulcer, 1.5 by 1 mm, no general reaction	28 days
7	Squash	32 days	—	Oats	—	Egg albumin	+	Squash Ulcer, 1.8 by 1.4 mm Slight general reaction (vomiting)	30 days

but in both cases soon recovered. When this was repeated the dogs, despite a polyphagia, went into the condition known as the cachexia of Arthus. This will be repeated on several dogs before we draw any conclusions as to its significance. Opie showed that the local reaction protected the individual from a general reaction by limiting the antigen to the site of the injection.

We had observed in our ulcer rabbits that the incision line invariably became necrotic. This occurred in the passively immunized rabbits also. But in the control gastric injections the abdominal incision lines just as invariably healed perfectly. We extended this observation to the pyloric pouch ulcers, in the light of Auer's conceptions by the method described above. Intraperitoneal injection of the antigen without the application of

TABLE 7—*Reinjections of Pylorus at Various Time Intervals in Dogs*

Dog	Specific Protein	Interval	Reaction	Intervals and Reaction
1	Casein	6 days	Dog vomited, local cyanosis and edema, healed in 2 days	1 day, nothing 2 days, nothing 3 days no vomiting cyanosis and edema, healed in 2 days
2	Ovis	4 days	Slight vomiting ulcer, 7 by 8 mm, healed in 20 days	1 day, nothing 21 days, nothing 4 days, nothing
		4 days	Soft infiltration, healed in 3 days	4 days, firm infiltration healed in 6 days 4 days firm infiltration, healed in 12 days 4 days, ulcer, 18 by 6 mm, healed in 20 days
4	Egg albumin	11 days	Severe general reaction prostration, defection, vomiting	1 day, nothing 2 days, nothing 3 days ulcer 4 by 4 mm healed in 10 days
		4 days	Ulcer, 5 by 5 mm, healed in 10 days	6 days slight general reaction ulcer, 2 by 2 mm 4 days ulcer, 7 by 6 mm 4 days old ulcer, 9 by 6 mm
		4 days	Old ulcer, 13 by 7 mm	4 days, older ulcer, 13 by 11 mm 4 days old ulcer 13 by 11 mm no reaction 12 days, new ulcer, 11 by 8 mm
5	Edestin	30 days	Nothing	4 days, nothing 4 days, soft infiltration, healed in 3 days 4 days, firm infiltration, healed in 6 days
		4 days	Hard infiltration healed in 11 days	4 days, ulcer, 6 by 9 mm 4 days, old ulcer, 12 by 9 mm 4 days, new ulcer, 11 by 7 mm
8	Beef	28 days	Nothing	4 days nothing 4 days, nothing 4 days, firm infiltration 7 days
		4 days	Firm infiltration, 10 days	4 days, ulcer, 7 by 6 mm 4 days, new ulcer, 5 by 5 mm 4 days, new ulcer, 5 by 4 mm
		4 days	New ulcer, 2 by 1 mm	4 days, no lesion 4 days, no lesion 4 days, new ulcer, 6 by 4 mm
9	Squash	11 days	Severe general reaction, no local	7 days, moderate general reaction, tiny ulcer 4 days, no general ulcer, 10 by 4 mm 5 days, slight general ulcer, 10 by 7 mm
		4 days	No general reaction old ulcer, 10 by 13 mm	4 days, old ulcer, 10 by 12 mm no reaction 12 days, new ulcer, 8 by 5 mm 12 days, severe general reaction no local
10	Egg albumin	20 days	Nothing	4 days nothing 4 days soft infiltration, 3 days 4 days, firm infiltration 7 days
		4 days	Firm infiltration, 18 days	4 days, ulcer, 9 by 8 mm 8 days, moderate general reaction, no local 4 days ulcer, 6 by 4 mm

xylene yielded nothing. Together with the application of the irritant to the old lesion, there was an aggravation of the old ulcer to some extent in most cases. The xylene itself had but slight effects. These last results were not sufficiently decisive to be conclusive, though they indicate corroboration of Auer's observations.

The production and course of the local anaphylactic ulcers produced in the gastric mucosa *in situ* was practically identical with that of the ulcers in the gastric mucosa of pyloric pouches. Healing time was not

TABLE 8—*Provocative Injection into the Gastric Mucosa in Situ in Dogs Without Pouches*

A Specific Injections After Intravenous Sensitization					
Dog	Date of Sensitization	Sensitizing Protein	Date of Gastric Injection	Date of Gastric Examination	Findings at Site of Injection
1	Nov 26	Egg albumin	Dec 30 (34)*	Jan 8 (9)	Ulcer in fundus, 7 x 7 mm Ulcer in pylorus, 5 x 3 mm
2	Oct 23	Egg albumin	Nov 17 (25)	Dec 17 (30)	Sear in fundus Sear in pylorus
3	Nov 26	Beef protein	Dec 30 (34)	Jan 8 (9)	Indurated mass in fundus Indurated mass in pylorus
4	July 29	Oat protein	Aug 17 (19)	Sept 14 (28)	Sear at pylorus
5	Nov 20	Horse serum	Dec 11 (21)	Dec 20 (9)	Ulcer at fundus, 3 x 3 mm Ulcer in pylorus, 4 x 8 mm
6	July 24	Horse serum	Aug 18 (25)	Sept 2 (15)	Ulcer in fundus Ulcer in pylorus
7	Nov 26	Edestin	Dec 26 (30)	Jan 2 (7)	Indurated mass in pylorus Indurated mass in fundus
8	July 24	Edestin	Aug 17 (24)	Sept 2 (16)	Ulcer in pylorus, 8 x 4 mm Ulcer in fundus, 6 x 6 mm
9	July 29	Squash	Aug 22 (22)	Sept 29 (40)	Sear at pylorus Sear at fundus
10	Dec 1	Squash	Dec 28 (28)	Jan 12 (15)	Ulcer in pylorus, 3 x 1 mm Ulcer in fundus, 7 x 5 mm
B Specific Injections After Sensitization by Other Routes					
11	Oct 23	Egg albumin subcutaneously	Nov 20 (27)	Dec 20 (30)*	Sear in fundus Sear in pylorus
12	Nov 3	Horse serum subcutaneously	Nov 24 (21)	Dec 20 (26)	Sear in fundus Sear in pylorus
13	Nov 26	Squash intraperitoneally	Dec 28 (32)	Jan 2 (5)	Ulcer in pylorus, 12 x 7 mm Ulcer in fundus, 15 x 9 mm
14	Nov 26	Edestin intraperitoneally	Dec 28 (32)	Jan 5 (8)	Indurated mass in fundus Indurated mass in pylorus
15	Nov 26	Beef protein intraperitoneally	Dec 23 (27)	Dec 31 (8)	Nothing in pylorus Nothing in fundus

* The figures in parentheses represent the interval in days since the preceding date in the table.

affected by the acid, the motility or whatever other factors were acting in the stomachs of these dogs.

The ulcers in the fundus were essentially identical with those in the pylorus. Any parenteral route was effective in sensitization. Not all the dogs were equally susceptible to sensitization. It should be noted that dogs 3, 7 and 14 gave only a three plus reaction, dog 15 none at all.

One defective result in our control injections was described above. The only other one occurred in control series A, table 9. A dog that had not been sensitized by us received a gastric injection of squash

seed globulin. An ulcer developed in the pylorus and in the fundus. The animal may have been spontaneously or artificially sensitized before. We cannot vouch for this. The control was repeated on four more dogs with negative results.

All our attempts to find precipitins in sensitized dog's serum by specific precipitation failed. We then made two attempts, one for beef protein and one for egg albumin, to demonstrate that the substances responsible for the local reaction were transmissible in the dog's serum. Three hundred cubic centimeters of whole blood was transferred by Kimpton-Brown-Percy tube from an animal that had been sensitized

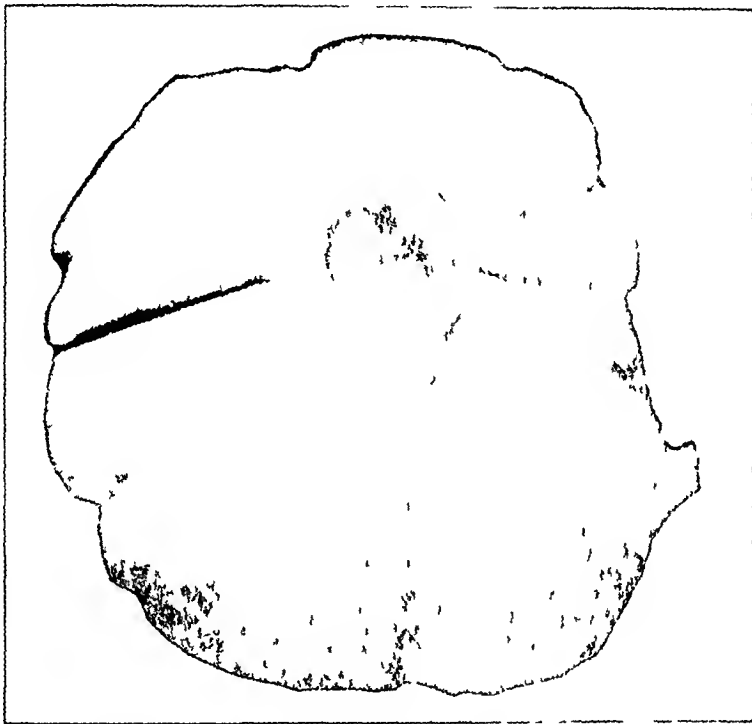


Fig. 9—Stomach of dog twenty-eight days after injection with oat protein, ulcer, at site of fundic injection, is 4 by 4 mm.

twenty-eight days before to an unsensitized animal. Forty-eight hours later, the recipient received a specific gastric injection which was uneventfully absorbed. A week later, the donor received a specific gastric injection which resulted in the usual ulcer at the pylorus and at the fundus.

COMMENT

The mechanism of local anaphylaxis is discussed in sufficient detail¹⁴. There is no indication that gastric local anaphylaxis differs essentially

¹⁴ Wells (footnote 10). Opie (footnote 6). Kolmer, J. A. Mechanism and Clinical Significance of Anaphylactic and Pseudoanaphylactic Skin Reactions, *Bull. Johns Hopkins Hosp.* **28** 163 (May) 1917. Coca, A. F. Mechanism of Anaphylaxis Reaction in the Rabbit, *J. Immunol.* **4** 219 (July) 1919. Weil, R. *J. Immunol.* **1** 19 (Feb.) 1916.

from cutaneous local anaphylaxis That our gastric reaction, like the skin reaction, is truly anaphylactic has been proved by conformity with most of Well's criteria (1) The toxicity of the injected material depends on sensitization of the animal—that is, these substances do not give similar symptoms in nonsensitized animals, (2) the symptoms are characteristic of typical soluble protein reactions, being the same for all the antigens with the same animal, but characteristic of the species, (3) the serum of sensitized animals effects passive sensitization, (4) desensitization follows recovery, and (5) specific precipitins have been demonstrated in the blood of sensitized rabbits

TABLE 9—*Control of Injections into the Gastric Mucosa in Situ in Dogs Without Pouches*

A Lesion Not Appearing in Absence of Previous Sensitization									
Dog	Sensitization	Date of Gastric Injection	Gastric Injection	Date of Gastric Examination	Findings at Sites of Injection				
16	None	Oct 23	Egg albumin	Oct 27 (4)*	Nothing in pylorus or fundus				
17	None	Nov 3	Horse serum	Nov 6 (3)	Nothing in pylorus or fundus				
18	None	Oct 27	Beef protein	Nov 1 (5)	Nothing in pylorus or fundus				
19	None	Oct 27	Edestin	Nov 1 (5)	Nothing in pylorus or fundus				
20	None	Nov 10	Squash	Nov 12 (2)	Nothing in pylorus or fundus				
B Reaction Required a Specific Sensitization									
Dog	Date of Sensitization	Sensitization	Date of Gastric Injection	Gastric Injection	Date of Gastric Examination	Findings at Sites of Injection			
21	Oct 23	Egg albumin	Nov 17 (25)*	Beef protein	Nov 20 (3)*	Nothing in pylorus or fundus			
22	Nov 3	Horse serum	Nov 24 (21)	Egg albumin	Nov 27 (3)	Nothing in pylorus or fundus			
23	Nov 20	Beef protein	Dec 23 (27)	Horse serum	Dec 28 (5)	Nothing in pylorus or fundus			
24	Nov 26	Edestin	Dec 28 (32)	Squash	Dec 31 (3)	Nothing in pylorus or fundus			
25	Nov 26	Squash	Dec 26 (30)	Edestin	Dec 28 (2)	Nothing in pylorus or fundus			

* The figures in parentheses represent the interval in days since preceding date in table

The failure to demonstrate satisfactory precipitin titer changes in dog's blood does not prove that their gastric hypersusceptibility is not anaphylactic The antibody may be so fixed in the tissue that the quantity in the serum is not comparable with that in the tissue Tissue immunity is not always parallel with serum antibody immunity

The negative tuberculin results may be ascribed (1) to the use of an anesthetic during the administration of the provocative dose (2) to a tissue peculiarity, for tuberculin gives a huge reaction in the testis, and (3) to the fact that the animals were sensitized to tubercle bacilli, not to tuberculin Though the Arthus phenomenon resembles the tuberculin reaction in some ways, Long¹⁵ distinguishes rigidly between local anaphylaxis and hypersensitiveness to infection Hypersensitive-

15 Long E R and Seifarth, M The Testicle as an Indicator of Allergy in the Hypersensitiveness of Infection and Anaphylaxis, *Am Rev Tuberc* 9: 259 (May) 1924

ness to tuberculin does not protect against tubercle bacilli¹⁶ as it would if tuberculin were a true specific antigen, and if the reaction were truly anaphylactic. The gastric tuberculin reaction in rabbits is comparable only to the skin reaction, but not to the testicular.

The negative casein results support the doubt cast by Seibert¹⁷ on the antigenic power of this protein.

Application of Local Anaphylaxis to the Etiology of Gastric Ulcer in Man—Gastric ulcer displays several striking etiologic phenomena. (1) The patient frequently is held to suffer from a general susceptibility to gastric ulcers, because the ulcers recur, extend and perhaps multiply—they appear in the absence of any demonstrable local cause. (2)

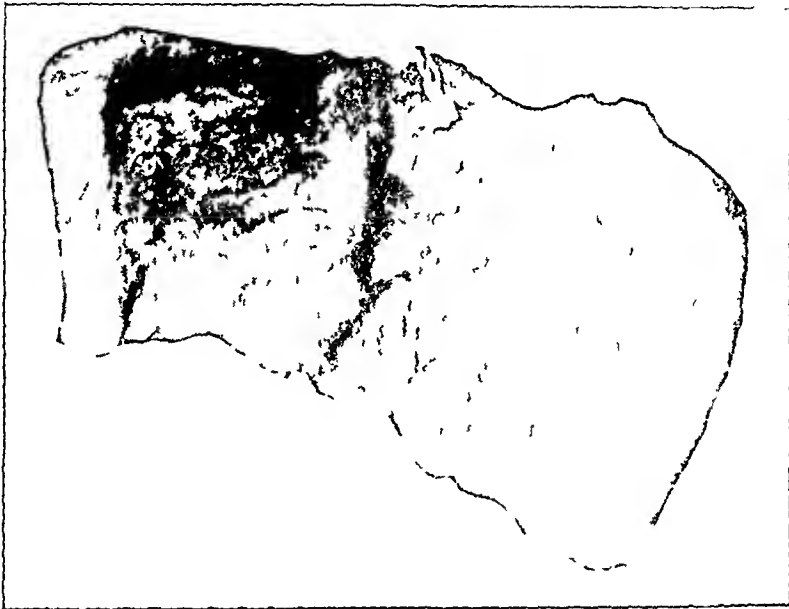


Fig. 10—Stomach of dog sensitized to horse serum seventeen days after local injection showing ulcer at pylorus.

with acid playing on the entire gastric mucosa only a slight area ulcerates, (3) the field of attack is almost exclusively localized to the pyloric antrum and duodenal cap, and (4) the lesions are acute and chronic.

These phenomena may be more or less closely simulated in the spontaneous production of ulcers by local anaphylaxis, provided our observations are applicable to man. That man becomes generally sensitive to foreign proteins is common knowledge. The specific protein is rubbed into the gastric mucosa. A local reaction arises at the site of this spontaneous specific injection, just as it arises in the diagnostic skin test for protein sensitization. But the gastro-intestinal mucosa reacts

16 Austrian, C. R. Effect of Hypersensitiveness to Tuberculin upon Subsequent Injection of Tubercle Bacilli. *Bull. Johns Hopkins Hosp.* **24**: 11-25, 1913.

17 Seibert, F. B., and Mendel, L. B. Protein Fevers. *Am. J. Physiol.* **67**: 105 (Dec.) 1903.

much more violently than does the skin, and instead of a little red wheal, necrosis and an ulcer develop. This may occur in the absence of any general symptoms. The local response protects the patient from a general reaction by limiting the antigen to the site of injection. After a period of desensitization, reinjection into the edges or base of the ulcer causes lateral extension or perforation. Reinjection into the vicinity produces a second ulcer.

The localization of the lesion in the pyloric ring region may be explained on the basis of the special mechanical and chemical conditions there prevailing. Beyond the duodenal cap, tryptic digestion and alkali racemization diminish or abolish antigenic powers of the proteins.



Fig 11—Ulcer at fundus in stomach shown in figure 10, photograph blurred by shrinking of specimen during exposure, specimen preserved in Kaiserling's solution

The digesting fundus of the stomach is comparatively atonic. The chances for rubbing protein in are therefore slight. At the pyloric ring, on the other hand, the proteins are still antigenic and can be readily rubbed into the mucosa by reason of the high motility, the spasms and the traumatism to which this region is subject.

Chronicity may be established in man by a repetition of local reactions until an irrevocable fibrosis develops. In the presence of specific antigen in the blood, coarse foods, hot drinks, acids and other non-specific irritants may suffice to elicit these local reactions, by locally concentrating antigen. Once a raw surface is made by an acute local anaphylactic reaction, direct acid digestion thereof may favor chronicity. Our observations support none of these factors in chronicity. We have produced acute lesions that heal slowly, but we have not satisfactorily demonstrated the chronicity of local anaphylactic ulcers in dogs.

How man would react we cannot say. Pribram has started treatment of gastric and duodenal ulcers by intravenous injection of a nonspecific protein¹⁸ (a water soluble plant albumin that he calls "novo-protein"). He gives doses of from 0.2 to 1 cc at three to four day intervals for about a month. He reports from 50 to 70 per cent good results. Injection is attended at first by a general reaction, a diagnostic local reaction,¹⁹ and an acute exacerbation of ulcer symptoms, later by healing. Hampel and Perutz insist that it be tried in every case of gastric ulcer before considering operative measures.²⁰



Fig 12—Section through ulcer shown in figure 7 ($\times 5$), examination at a higher magnification shows a mild inflammatory reaction in and about the base of the ulcer, the connective tissue proliferation should be noted

SUMMARY AND CONCLUSIONS

1 Acute gastric ulcers were experimentally produced on the basis of local anaphylaxis to specific antigens. Passively immunized animals yielded the same gastric lesions.

2 Healing time of the acute ulcers in rabbits was about twelve days, one not being healed at thirty-three days, and in dogs from about twenty-one to thirty days, one not being healed at thirty days. This demonstrates that these ulcers appear to become chronic in some instances.

18 Pribram, B. O. Parenteral Protein-Irritation Therapy of Gastric and Duodenal Ulcers, *Med Klin* **30** 958-960 (July 23) 1922.

19 Weiss. Diagnosis of Peptic Ulcer with Protein Injections, *Deutsche med Wchnschr* **49** 1110 (Aug 24) 1923.

20 Hampel. *Med Klin* **19** 781-816 (June 10) 1923. Perutz. *Munchen med Wchnschr* **70** 1527-1528 (Dec 28) 1923.

3 A period of desensitization followed production of the acute lesion. After this period reinjection yielded another ulcer or caused extension of the first. This was repeated until the mucosa was riddled with ulcers or was occupied by a single large ulcer. Continued reinjection of the ulcer at from three to five day intervals progressively desensitized the dog while it slightly delayed healing of the original lesion.

4 The local reaction limited the antigen to the site of injection, thus preventing a general reaction. Diminution of the local reaction was associated with an increase in the general reaction. Both local and general hypersensitiveness gradually diminished with time, but could be again elicited by local or general reinjection.

5 The anaphylactic nature of the local gastric reaction, like that of the cutaneous, has been established in rabbits. In rabbits the severity of the gastric reaction has been shown to parallel the precipitin titer of the serum. Our data has conformed with most of Well's criteria for anaphylaxis.

6 Precipitins to plant or to animal proteins could not be detected in sensitized dogs' serums.

7 The severity of the local reaction was characteristic of the particular tissue in which it occurred, and of the species of animal involved. Wide differences were observed here. In dogs the gastric reaction was more severe than the cutaneous, in rabbits the cutaneous reaction was more severe than the gastric.

8 Ulcers produced in the fundus were practically identical with those in the pylorus.

9 Motility and other intragastric factors had no effect on the healing time of these ulcers.

10 Positive results were obtained in rabbits and dogs with egg albumin, beef protein, oat protein, squash seed globulin, edestin, hemoglobin and horse serum, negative results with casein, milk and tuberculin.

11 Controls to the mediums of injection and to nonspecific proteins were negative.²¹

21 At the conclusion of our work a reference appeared in the *Journal of the American Medical Association* to some work by M. Loeper and G. Marchal on 'local anaphylactic ulcers' (Effect of Sugar on the Stomach, *Bull. Soc. med. d. hop. de Paris* 49:721-771 [May] 1925). The original article, like that of Havashi, revealed no relation at all to anaphylaxis, but again showed simply a matter of drug hypersensitiveness. They had observed simply that the gastric mucosa of certain persons was particularly susceptible to ulceration following the administration of acetyl salicylic acid and antipyrine. They found that the simultaneous administration of sugar prevented the formation of gastric lesions.

THE UNITARY NATURE OF IMPAIRMENT OF RENAL FUNCTION

ARTHUR M. FISHLER, M.D.
NEW YORK

Nearly a century has elapsed since Richard Bright made his celebrated "statements and conjectures regarding the dependence of a peculiar class of Dropsies on disease and irritation of the Kidneys"¹ Since then numerous additions have been made to our knowledge of the symptomatology of Bright's disease, the most significant, perhaps, being arterial hypertension, albuminuric icteritis and the so-called uremic phenomena largely involving the central nervous system. The systemic manifestations of kidney disease are so variegated, and their association with one another so inconstant, that it was early realized they could not all be due to the same pathogenetic factor. In attempts to explain the connection between the kidney lesions and the associated systemic phenomena, two main paths have been pursued:

1 The study of extrarenal factors. This dates back to the classic investigations of Gull and Sutton² on cardiac hypertrophy and Cohnheim and Lichtheim³ on edema. In the case of uremia the pathogenetic significance of extrarenal moments has been emphasized only comparatively recently, particularly by Vaquez⁴ and Volhard.⁵

2 The introduction of the concept of isolated injury to individual functions of the kidney, the so-called "partial functions" while the other excretory functions are satisfactorily performed, leading to selective retention. This conception was inaugurated by Widal⁶ and Strauss⁷ in 1902. They found that in uremia there is deficient excretion of the nonprotein nitrogenous constituents of the blood while in edema sodium chloride is not adequately eliminated. As a result of these studies there arose the division, on a functional basis, of the various forms of Bright's disease into two great groups: (1) the cases in which sodium chloride

* From the medical division of the Montefiore Hospital.

1 Bright. Reports of Medical Cases, London 1827, preface, p. viii.

2 Gull and Sutton. On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease, Tr. Med-Chir. Soc. 55: 273, 1872.

3 Cohnheim and Lichtheim. Ueber Hydræmie und hydræmisches Oedem. Virchows Arch. f. path. Anat. 69: 106, 1877.

4 Vaquez. Maladies du Cœur. Paris 1921, p. 498.

5 Volhard, Mohr, and Staehelin. Handbuch der inneren Medizin, Berlin 3: 1314, 1918.

6 Widal and Javal. La dissociation de la perméabilité du rein pour le chlorure de sodium et l'urée dans le mal de Bright. Compt. rend. Soc. de biol. 55: 1639, 1903.

7 Strauss. Die chronischen Nierenerkrankungen in ihrer Einwirkung auf die Blutflüssigkeit, Berlin, 1902.

is retained, clinically characterized by edema, and (2) the group in which nitrogenous bodies are retained, showing a tendency to uremia. This subdivision has found wide favor, the two groups being known in this country as nitrogen retaining and chloride retaining, in France as uremigenic and hydropigenic, and in Germany as hypazoturic and hypochloruric. It is everywhere recognized that combinations of the two types are very common. Further study⁸ of the nitrogen retaining type in this country has led to the claim that as the kidney fails impairment of excretion of the individual nonprotein nitrogenous constituents of the blood occurs at successive periods, the first retained being uric acid, next urea, and finally creatinine.

In this article we desire to present evidence that no matter what its anatomic substratum, impairment of renal function is manifested by injury to *all* the excretory functions of the kidney, and that when selective retention occurs in Bright's disease, it is not due to inability of the kidney to excrete the retained substance, but to intervention of an extrarenal factor.

BLOOD CHEMISTRY IN UREMIA

It was mentioned in the foregoing that the differentiation of the nitrogen retaining form of kidney disease dates from the demonstration by Widal and Strauss that the concentration of nonprotein nitrogen in the blood is increased in uremia. In these cases the chloride content of the blood was shown to be normal. These researches furnished the chemical explanation of von Koranyi's⁹ earlier finding that in uremia the freezing point of the blood serum is lower than normal, but that the conductivity of the serum is normal, i. e., that the total molecular concentration is increased but not the concentration of the electrolytes. At the time only nonprotein nitrogen, urea and chloride could be determined accurately in the small quantities of blood available clinically. Since then methods have been developed particularly in this country, for the estimation of numerous other substances in small volumes of blood. With these micromethods blood chemistry in uremia has been exhaustively studied and the following findings relevant to the present topic may be taken as definitely established.

The nitrogenous bodies urea, uric acid and creatinine are increased in the blood in true uremia. It has been stated⁸ that uric acid accumulates before the others. However isolated increase in the uric acid content of the blood in the presence of normal urea values in a hypertensive patient

⁸ Myers, V. C., Fine, M. S. and Lough, W. G. The Significance of the Uric Acid, Urea and Creatinine of the Blood in Nephritis, *Arch. Int. Med.* **17**: 570 (April) 1916.

⁹ Von Koranyi. Physiologische und klinische Untersuchungen über den osmotischen Druck thierischer Flüssigkeiten. *Ztschr. f. klin. Med.* **33**: 1, 1897, **34**: 1, 1898.

is not due to renal failure but is a metabolic phenomenon correlated with the hypertension¹⁰ Such hyperuricemia cannot, therefore be considered as an example of selective retention

Indican, phenol, and aromatic oxyacids¹¹ are found in increased concentration in the serum in renal failure Indican, the best studied, may accumulate to a concentration of 1 mg per hundred cubic centimeters, the normal being about 0.05 mg per hundred cubic centimeters Its amount, however, varies greatly, due to alterations in the source of supply (intestinal putrefaction)

The phosphate content of the serum may be increased to over ten times the normal

The sulphate concentration of the serum may be increased to over twenty times the normal¹²

Potassium is only moderately increased, the highest figure I have seen in the literature is 36 mg per hundred cubic centimeters¹³ the normal being 20 mg

TABLE 1—*Blood Chemistry in Uremia*

Increased		Not Increased	
Urea	Phosphate	Chloride	Calcium
Uric acid	Sulphate	Sodium	Water
Creatinine	Urochromogen	Magnesium	Ammonium (discussed in text)
Indican	Potassium (slightly)		

Urochromogen retention in the serum has been demonstrated by Becher,¹¹ thus explaining the light color of the urine even in the absence of polyuria

The urinary constituents, chloride, sodium, magnesium, calcium and water, are not increased in the blood in uremia, in fact, chloride and calcium are often present in subnormal concentrations Water is not retained as a result of renal insufficiency per se (discussed later) and therefore belongs in this group, though we are not accustomed to speaking of it in terms of "concentration"

From the standpoint of blood chemistry, then, the urinary constituents may be divided into the two groups given in table 1, the criterion being whether or not their concentration in the blood is increased when the kidney fails

10 Fishberg, A. M. The Interpretation of Increased Blood Uric Acid in Hypertension, *Arch. Int. Med.* **34** 503 (Oct.) 1924

11 Becher, E. Studien über Chromogene im Serum und Harn von Nierenkranken, *Deutsches Arch. f. klin. Med.* **148** 46 (Juli) 1925

12 Denis, W., and Hobson, S. A Study of the Inorganic Constituents of the Blood Serum in Nephritis, *J. Biol. Chem.* **55** 183 (Feb.) 1923

13 Briggs, A. P. A Study of the Inorganic Elements of the Blood Plasma *J. Biol. Chem.* **57** 351 (Sept.) 1923

The chemical composition of the blood thus resulting constitutes the "chemical blood picture" of renal insufficiency. What is the reason that certain urinary constituents increase in the blood in renal insufficiency, while others do not? The following explanations are widely held

1 The explanation generally advanced is that only certain functions of the kidney involving the excretion of the substances accumulating in the blood are injured, while the power of the kidney to eliminate the bodies present in normal concentration is unimpaired. It will be shown shortly that this opinion is fallacious and that when renal function is impaired *all* the excretory functions of the kidney are injured.

2 It may be thought that those substances whose concentration in the blood in renal insufficiency is not increased are really retained, but that they are stored in the tissues and not in the blood. In the case of sodium chloride, this is often presumed to lead to a secondary retention of water with the formation of edema. But as most cases of uremia in chronic Bright's disease show no edema whatsoever, or merely an obviously "cardiac" edema, and often the tissues are plainly dehydrated, it has been assumed that sodium chloride may be retained in the tissues without corresponding retention of water, the retention *seche* (dry retention) of Ambard and Beaujard¹⁴. But that *actual retention of chloride in nonedematous patients is manifested by a rise in the chloride concentration of the blood* is shown by instances of complete or almost complete anuria due to mechanical obstruction of the urinary passages in which the patient continues to ingest chloride as usual. In such cases of mechanical anuria, in which chloride continues to be ingested, we often see the blood chloride concentration rise to very considerable heights. Thus, in a case of carcinomatous obstruction of both ureters the plasma chloride concentration rose to 1100 mg per hundred cubic centimeters (as sodium chloride) in a case of cystitis and ureteritis following a spinal cord lesion to 950 mg and in a patient in whom the ureters had been implanted in the abdominal wall and then become obstructed to 738 mg. Similar instances have been published by Braasch¹⁵ and others, in one of Braasch's cases the plasma chloride attained the enormous height of 1,500 mg per hundred cubic centimeters.

There seems to be no reason for believing that retention caused by mechanical blockage of the urinary passages affects the concentration of a substance in the blood differently than does an equal retention due to disease of the kidney itself. We would, therefore, expect that if chloride were retained in Bright's disease to the same extent as in these cases of mechanically caused anuria the concentration of chloride in the blood

14 Ambard and Beaujard. La retention chloruree seche, *Semana med*, 1905, p 133

15 Braasch. Ueber die klinischen Erscheinungen bei langdauerender Anurie, *Deutsches Arch f klin Med* 103 488 1911

would rise as it does in the anuria of obstruction. The fact that in uremia terminating chronic Bright's disease the concentration of chloride in the blood is not increased, but in fact often decreased, speaks strongly against the existence of chloride retention in these nonedematous uremic patients.

It thus seems clear that neither selective injury to individual functions of the kidney nor extravascular storage in the tissues explains the chemical picture of the blood in uremia, in which certain substances, e. g., urea, accumulate, while others, such as chloride, do not increase in concentration. The explanation, we believe, is purely quantitative. In the quantitative study of renal insufficiency three factors must be considered:

- 1 The concentration ratios of the individual urinary constituents
- 2 The possibilities for extra-renal excretion of the individual urinary constituents

TABLE 2—*Concentration of Substances by Kidney*

Substance	Concentration in Urine, M _L per Cent	Concentration in Blood, M _L per Cent	Number of Times Con- centrated	Concentration in Blood in Renal Insufficiency
Urea	2,000	30	65	Increased
Uric acid	60	2	30	Increased
Creatinine	75	2	35	Increased
Indican	1	0.05	20	Increased
Phosphate	150	3	50	Increased
Sulphate	150	1	40	Increased
Potassium	150	20	7	Slightly increased
Chloride	500	350	1.5	Not increased
Sodium	50	300	1	Not increased
Calcium	15	10	1.5	Not increased
Magnesium	6	3	2	Not increased
Water			1	Not increased

3 Variations in the amounts of the individual urinary constituents brought to the kidney

1 *Concentration Ratios*.—The work of the kidney consists almost entirely in a highly selective concentration and elimination of various constituents of the blood. If one compares the number of times the individual urinary constituents are concentrated by the kidney, it will be noted that there is a sharp difference between the substances which increase in concentration in the blood in uremia and those which do not (table 2).

From table 2 it is seen that those substances which accumulate in the blood in renal insufficiency are precisely the ones that are highly concentrated by the kidney, while the bodies with a normal level in the blood of the uremic patient are the ones whose average concentration in the urine is little or not at all greater than that in the blood. The urinary ammonium forms an obvious exception, being, in all probability, formed almost entirely by the kidney and not a simple excretion from the blood,

it is therefore omitted from table 2 Potassium, which undergoes only slight concentration, shows a comparatively small increase in the blood as a result of severe renal insufficiency

The explanation of this parallelism between the degree of concentration of a substance by the kidney and its accumulation in the blood in renal failure would seem to be the following

Let us consider those substances which are excreted almost entirely in the urine The absolute amount of each of these substances eliminated in a twenty-four hour period is obviously proportional to its average concentration in the urine of that time Also, in the presence of normal kidney function, the amount of each substance in the day's urine is equal to the amount that the tissues throw into the blood for excretion during that period If, now, complete cessation of renal activity occurs, while ingestion and metabolism go on unchanged, the substances which should be excreted by the kidney will accumulate in the blood in amounts that are proportional, as just shown, to their respective average concentrations in the urine And the number of times a substance increases in concentration in the blood will be proportional to this quantity (the average concentration in the urine) divided by the initial concentration in the blood In other words, the normal value of the ratio average concentration in urine concentration in blood is a measure of the number of times a substance will increase in concentration in the blood if renal insufficiency sets in, provided extrarenal factors remain unchanged To illustrate The concentration ratio for urea is $\frac{2,000 \text{ mg per hundred cubic centimeters}}{30 \text{ mg per hundred cubic centimeters}} = 65$ and for chloride $\frac{500 \text{ mg per hundred cubic centimeters}}{350 \text{ mg per hundred cubic centimeters}} = 1.5$ Therefore, if renal function is completely inhibited, under the ideal conditions of unchanged ingestion and metabolism, the concentration of urea will multiply in the blood $\frac{65}{1.5} = 43$ times as rapidly as will the concentration of chloride And if it takes one day for the urea concentration of the blood to double, it would take forty-three days to double the chloride concentration

Calculations such as the foregoing can be only rough approximations at the best, for they do not take into consideration the possibility that the distribution of different substances between blood and tissues may be differently affected by retention But the foregoing considerations do serve to indicate why it is so much more difficult for renal insufficiency to raise the level in the blood of a substance like chloride, which is little concentrated by the kidney, than of the highly concentrated urea

2 *Extrarenal Excretion*—In studying the blood chemistry of renal insufficiency, it must be remembered that certain of the urinary constituents may also be excreted by channels other than the urine Thus, under normal circumstances about 40 per cent of the total water excre-

tion is eliminated extrarenally¹⁶ Likewise, probably the greater part of the calcium and magnesium is eliminated through the bowel From what we know of the factor of safety with which almost all of the bodily functions are endowed, it is obvious that in the case of these substances elimination will be completed by vicarious activity of the respective extrarenal organs of excretion despite complete cessation of activity of the kidney The kidney can quickly eliminate a large quantity of water, but under ordinary circumstances where speedy elimination is not required, the lungs and skin can excrete the necessary amount of water It is thus readily understandable why, despite numerous past assertions to the contrary, recent investigations¹⁷ with more adequate methods have not revealed an increase in the blood volume in chronic renal insufficiency In the case of other substances, however, such as the nitrogenous constituents of the urine and chloride, the proportion eliminated extrarenally is small and cannot be increased sufficiently to compensate for defective renal function So in the case of these substances, extrarenal elimination will not suffice to prevent accumulation in the blood

3 *Variations in Supply*—Not must we think of the urinary constituents solely from the point of view of excretion Alterations in the source of supply must be considered With the exception of potassium, all the substances in the group that increases in renal insufficiency are obligatory and products of the catabolism of tissue proteins, and while they may be diminished in amount by the elimination of protein from the diet, they continue to be produced in considerable quantity under all circumstances from the breakdown of tissue protein On the other hand, the group of substances that do not increase in renal insufficiency can be caused almost to disappear from the urine by eliminating them from the dietary So that from this standpoint there also is a significant difference between the two groups, in that by a suitable dietary we can almost remove the necessity for the excretion of the substances of the second group, but this is not feasible in the case of the protein derivatives It is thus readily comprehensible why such substances as chloride do not show even a slight increase in the blood of patients with chronic uremia, but more often an actual decrease, it is because these patients have been kept on a salt-poor diet furnishing even less chloride than the severely injured kidney can excrete Moreover, there is often a considerable loss of chloride by vomiting

16 Roth, N. Beiträge zum extrarenalen Wasserstoffwechsel bei Normalen und Nephritiden, *Ztschr. f. klin. Med.* **98** 305 (March) 1924

17 Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillmann, E. G. Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, *J. Exper. Med.* **39** 921 (June) 1924. Brown, G. E., and Rowntree, L. G. The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, *Arch. Int. Med.* **35** 129 (Jan.) 1925

A special position is occupied by those urinary constituents (hippuric acid, ammonium) which are formed by the kidney itself. These, it would be expected, should not accumulate in the blood in renal insufficiency, and it has in fact been shown¹⁸ that in uremia the ammonium content of the blood is normal and that of the urine diminished.

THE URINE IN IMPAIRED RENAL FUNCTION

It has long been known that when renal function is impaired the specific gravity of the urine is low and cannot be raised by any of the agencies, such as restriction of fluids, profuse sweating and cardiac failure, under the influence of which a normal kidney elaborates a highly concentrated urine. It was shown by von Koranyi⁹ that the low specific gravity of the urine is due to a decrease in the total molecular concentration, for the depression of the freezing point is less than normal. As the freezing point and therefore the osmotic pressure of the urine in renal injury tend to remain constant near that of the blood serum, he termed the condition isosthenuria.

We have studied the concentrating power of the kidney, using the technic described below for the concentration test, and have found the characteristics of the urine in chronic impairment of renal function, as regards the specific gravity, urea, and chlorid concentrations, to be the following.

Specific Gravity—As is well known, the maximum specific gravity of the urine falls progressively as the kidney fails and forms a measure of the functional capacity of that organ. (By maximum specific gravity is meant the highest specific gravity reached in the concentration test.) The lowest point to which the maximum specific gravity attainable by sufficiently prolonged deprivation of fluid falls is 1.010. We have reference, of course, only to nonedematous patients, for in the presence of resorbing edema it is often impossible to ascertain the maximum concentrating power of the kidney, owing to a constant supply of water from the edema fluid. Only in isolated instances have we been unable to attain a specific gravity of 1.010 by the thirst procedure, and in these the maximum was either 1.008 or 1.009.

We have not seen a single instance of true chronic uremia¹⁹ in which the maximum specific gravity of the urine was not under 1.020.

18 Russell. Ammonia Content of the Blood in Nephritis, *Biochem J* **17** 72, 1923.

19 The term uremia is used, following Volhard,⁵ for a group of symptoms resulting from retention of urinary constituents and therefore always found in association with renal insufficiency, these symptoms occur most typically in anuria due to mechanical obstruction. It will bear repetition that by no means all the nervous phenomena occurring in the course of Bright's disease are uremic in nature, but that convulsions, amaurosis, transient palsies, etc., may occur in the presence of intact renal function, being in some way correlated with the hypertension.

almost always under 1.015. In cases of uremia terminating chronic Bright's disease in which the highest specific gravity attainable was between 1.015 and 1.019, there was always evidence of marked myocardial insufficiency. In azotemic patients without well marked myocardial insufficiency, the maximum specific gravity was below 1.015, terminating in inability to concentrate above a specific gravity of 1.010. Recently, we were able to examine the last 50 cc. of urine eliminated by a patient dying of uremia without any evidence of myocardial insufficiency, i. e., a purely "renal" death, and found the specific gravity to be 1.010. Necropsy revealed a primarily contracted kidney complicated by slight bilateral pyonephrosis. The wall of the left ventricle was greatly thickened, but there was no evidence of dilatation, the chamber of the left ventricle being very small. It would seem that maximal impairment of renal function (apart from total anuria) is characterized by inability of the kidney to elaborate a urine of concentration higher than that represented by a specific gravity of 1.010.

Urea—The fact that patients whose renal function is defective have impaired concentrating power for urea has been used by Maclean²⁰ as the basis of his well known urea concentration test. Using the concentration test as described below, we have found that patients with maximal impairment of concentration, i. e., with a maximum specific gravity of 1.010, cannot elaborate urine containing more than 0.9 per cent of urea, and the maximum is usually much less. Under these conditions a normal kidney readily concentrates urea to over 2 per cent.

Chloride—The maximum concentration of chloride in the urine of patients with impaired renal function is more difficult to ascertain than that of urea because of the frequent complication by myocardial insufficiency which, as is well known, greatly reduces the concentration of chloride in the urine, even though the kidney is normal. If the patient has been on a salt-poor diet for some time, it is difficult to find the maximal renal insufficiency (maximum specific gravity, 1.011), the avidity of the tissues for salt. We have found that in instances of maximally renal insufficiency (maximum specific gravity, 1.010), the highest concentration of chloride attainable is always low, the highest we found was 0.42 per cent (calculated as sodium chloride), and in many instances we were unable to obtain nearly so high a concentration. Under similar conditions the normal kidney produces urine containing over 1 per cent, often over 1.5 per cent sodium chloride. In accord with this, De Wesselow²¹ has recently found that "the kidney in interstitial nephritis shows, when examined by a chloride concentration test, an

20 Maclean. *Modern Methods in the Diagnosis and Treatment of Renal Disease*, Ed. 2, Philadelphia, 1924, p. 59.

21 De Wesselow, O. L. V. *The Excretion of Chlorides by the Healthy and Diseased Kidney*, *Quart. J. Med.* **19**: 53 (Oct.) 1925.

inability to concentrate chlorides running parallel with the failure of the capacity to concentrate urea" Despite this impairment of the ability to concentrate chloride there is no chloride retention in chronic renal insufficiency for reasons given in the foregoing But Veil²² has shown that retention with a marked rise in the concentration of chloride in the blood may be produced in renal insufficiency by the ingestion of excessive amounts of chloride

Studies on the concentration of calcium in the urine in impaired renal function have been carried out recently by Hetényi and Nógrádi²³ They found that when renal function is impaired the ability of the kidney to concentrate calcium is greatly diminished Nevertheless, in the case of calcium as in that of chloride, we have seen that there is no retention, for calcium is a substance that is normally but slightly concentrated by the kidney, and is also excreted by the intestine in probably even larger quantities than by the kidney

CHLORIDE RETENTION

There are many instances of Bright's disease in which the outstanding clinical manifestation is edema These are the cases that are generally known as the "chloride retaining" form, and it is widely believed that in these instances there is specific injury to the ability of the kidney to excrete sodium chloride The explanation of the edema as due to impairment of the power of the kidney to excrete salt is largely based on the fact that the urine of such patients contains little sodium chloride, and that in certain edematous patients with Bright's disease—as in the classical case of Widal and Javal⁶—it is possible to increase or decrease the edema at will by feeding or restricting sodium chloride

Glomerulonephritis may present for a long time the picture of isolated chloride retention, but this may at any time be complicated by the development of nitrogen retention, thus producing a "mixed" case The classical picture of isolated chloride retention is seen in lipoid nephrosis In these cases, anatomically characterized by purely degenerative lesions of the tubules of the kidney, there is no evidence of any injury to kidney function The urine is of high specific gravity, the nonprotein nitrogen and chloride of the blood are not increased, the Ambard constant and urea concentration tests are normal, and dyes are excreted promptly That the low concentration of sodium chloride in the urine in nephrosis is not due to a specific inability of the kidney to excrete salt is proved by the diuresis with a high concentration of sodium

22 Veil Ueber die Bedeutung intermediaerer Veraenderungen im Chlorstoffwechsel beim Normalen und beim Nierenkranken, *Biochem Ztschr* 91 299, 1918

23 Hetenyi, G, and von Nógrádi, S Ueber die Kalkausscheidung der gesunden und kranken Niere, *Klin Wchnschr* 4 1308 (July 2) 1925

chloride in the urine often initiated by Epstein's²⁴ treatment with high protein feeding and the administration of thyroid, measures that surely do not serve to improve the concentrating power of the kidney. That chloride retention in itself does not cause any considerable edema is proved by cases of mechanical anuria with high blood chloride concentration (described above) which do not present edema. The primary cause of the edema in Bright's disease has been shown by numerous researches in recent years to be extrarenal, in nephrosis being correlated with the low protein content of the blood (Epstein) and in nephritis possibly with changes in the capillary walls.

The low concentration of sodium chloride in the urine—sometimes there may be only mere traces present—is, I believe, explained by the fact that the concentration of sodium chloride is higher in the transudates than in the blood, which serves to reduce the concentration of sodium chloride in the blood to near the threshold value and thereby inhibits its excretion. In other words, the diminished excretion of chloride is not the cause of the edema but the result of it, and to consider edematous types of Bright's disease as examples of selective injury to one of the functions of the kidney (sodium chloride excretion) is erroneous. The "pure" picture of chloride retention is produced by the combination of an extrarenal cause for edema with intact kidney function, though of course impairment of renal function may also be present or supervene at any time, thereby producing a mixed case.

ANATOMIC BASIS AND NATURE OF IMPAIRMENT OF RENAL FUNCTION

It has been seen that when the kidney fails in chronic Bright's disease, this failure is always manifested in the same way, namely, by a lowering of the maximum concentrations of the individual urinary constituents. If the impairment of renal function progresses, the maximum specific gravity attainable falls further and further, till the most concentrated urine that the kidney can elaborate is that with a specific gravity of 1.010, which is approximately the specific gravity of deproteinized blood serum. It was also seen that in cases in which chloride alone is retained, the urine has a normal or high specific gravity and there is no impairment of renal function.

We have studied the blood and urine in uremia due, not to Bright's disease, but to the so-called surgical diseases of the kidney and urinary passages. The material studied comprised cases of uremia caused by

Prostatic enlargement

Paralysis of the bladder in tabes

Polycystic kidneys

Pyelonephrotic and tuberculous destruction of the renal parenchyma

²⁴ Epstein, A. A. Further Observations on the Nature and Treatment of Chronic Nephrosis, *Am J M Sc* **163** 167 (Feb.) 1922

It was found that, apart from instances of total anuria (described above), the changes in the blood and urine are identical with those just described as occurring in the uremia of Bright's disease. Just as in Bright's disease, there is progressive diminution in the concentrating power of the kidney, ending in inability to elaborate a urine of specific gravity above 1.010, which is light in color and contains less than 0.9 per cent urea and 0.45 per cent sodium chloride. As long as water is in any way available, even by dehydrating the tissues, there is polyuria in an effort to compensate for the loss of concentrating power. In the blood, those substances such as urea, which are highly concentrated by the kidney increase in amount while the chlorides are normal or even markedly diminished except in total anuria as noted above, and there is acidosis, presumably largely from phosphate retention. The following are typical examples.

G. K. had bilateral polycystic kidneys. The systolic blood pressure was 210, diastolic 100. Concentration and dilution tests revealed a maximum specific gravity of 1.010 and a minimum of 1.008. The phenolsulphonphthalein output was less than 1 per cent. Blood analysis revealed nonprotein nitrogen, 133.3, urea nitrogen, 113.4, uric acid, 4.5, and creatinine, 4 mg. per hundred cubic centimeters, plasma chlorides, 590 mg. of sodium chloride per hundred cubic centimeters, and carbon dioxide combining power, 26 per cent by volume.

A. L. had nephrolithiasis, bilateral ureteritis and pyelonephrosis. The maximum specific gravity was 1.010, and the phenolsulphonphthalein output almost 0. Blood analysis revealed nonprotein nitrogen, 136.5, urea nitrogen, 75.6, uric acid, 5.2, and creatinine, 3.6 mg. per hundred cubic centimeters, plasma chlorides, 420 mg. per hundred cubic centimeters (as sodium chloride). The patient died from uremia.

In prostatic hypertrophy the concentrating power often returns so rapidly after the obstruction has been relieved that it seems probable that the impairment of renal function is not due to organic changes in the kidneys. In a tabetic patient with paralysis of the bladder and the typical blood and urine changes of renal insufficiency (maximum specific gravity, 1.012), renal function was quickly restored by the insertion of an indwelling catheter, but concentrating power was again lost after the catheter had been removed for some time.

The foregoing would seem to indicate that no matter in which way the kidney is diffusely injured—whether by inflammatory or arteriosclerotic changes, by cystic transformation and compression in polycystic kidneys, or by increase of urinary pressure starting from obstruction of the urinary passages—impairment of renal function is always manifested in the same way, namely, by a lowering of the maximum concentration in which the individual urinary constituents can be eliminated thereby producing the typical "chemical picture" in the blood and urine described above. So far as we know there is only one variety of impaired renal function—that in which all the excretory functions are injured—and

impairment of renal function may vary quantitatively but not qualitatively

It is therefore justifiable to speak of impaired renal function as renal hypofunction. It is important to realize clearly the difference between renal hypofunction and renal insufficiency. Renal insufficiency is the analog of cardiac insufficiency and means that because of defective kidney function the necessary quantity of waste products is not being excreted. The criterion of renal insufficiency is the accumulation of excretory products in the organism, just as the criterion of cardiac insufficiency is the presence of such conditions as dyspnea and edema. On the other hand, renal hypofunction means only that renal function is impaired, though excretion may be completely performed by a compensatory mechanism (polyuria) and the organism as a whole does not suffer. The criterion of renal hypofunction is loss of concentrating power. The concept of renal hypofunction is broader than, and inclusive of, the concept of renal insufficiency.

In this connection, it may be recalled that Ambard²⁵ has claimed that the maximum concentrations of the various urinary constituents are isotonic with one another, and that a reduction in one is accompanied by a proportional reduction in the others. Whether or not this generalization has exact quantitative validity, we are not in a position to judge.

It is difficult to explain why such anatomically variegated injuries to the excretory functions of the kidney are all manifested by a decrease in the concentrating power, the extreme of which is in all cases at the same concentration (maximum specific gravity, 1.010). The old experiments of Bradford²⁶ showed that ablation of the greater portion of the renal parenchyma causes a polyuria with low specific gravity like that of impaired renal function in man. Richards²⁷ has demonstrated that only a fraction of the total number of glomeruli function at the same time. And Rabinowitch²⁸ has calculated that it takes less work to eliminate a gram of any substance in dilute solution than in a more concentrated solution. On the basis of these findings, a teleologic interpretation of the low concentration of the urine occurring in widespread renal injury may be advanced. It may be considered that the remaining kidney elements, having less rest, always elaborate urine in the most economical manner as regards actual work performed, which is in dilute

25 Ambard. *Physiologie normale et pathologique des reins*, Ed 2, Paris, 1920, pp 185-188.

26 Bradford. The Influence of the Kidney on Metabolism, *Proc Roy Soc London* **51** 25, 1892.

27 Richards, A. M. Kidney Function, *Am J M Sc* **163** 1 (Jan) 1922.

28 Rabinowitch, I. M. A Quantitative Index of Kidney Function, Thermodynamic Considerations in Estimation of Renal Efficiency, *Arch Int Med* **34** 365 (Sept) 1924.

solution. But teleologic interpretations in medicine are always risky. Nevertheless, it seems significant that in the severest impairment of renal function, the maximum specific gravity of the urine does not fall below 1.010, at which level the osmotic pressure of the urine approximates that of the blood. However, even in urine of specific gravity 1.010, the maximum urea concentration is still many times that of the blood, while the maximum chloride concentration is less than that of the blood. Such differences are difficult to interpret.

COMPENSATION AND DECOMPENSATION IN RENAL HYPOFUNCTION

Since the functionally impaired kidney is unable to elaborate a concentrated urine, it can meet an increased demand only by increasing the volume of the urine, and as the injury to the kidney progresses polyuria becomes necessary to eliminate the waste products even from a basal diet. The polyuria of renal hypofunction is a true compensatory mechanism comparable to the cardiac hypertrophy following a valvular lesion. The stage in which there is impairment of the concentrating power of the kidney and yet excretion is completely performed through the mechanism of polyuria may be termed the stage of compensated renal hypofunction. Such cases may go into the stage of decompensated renal hypofunction, marked by retention of urinary constituents in the blood, if the volume of urine diminishes. This reduction in the polyuria may be due to myocardial weakness resulting from the hypertension, or to injury to so large a proportion of the glomeruli that the necessary amount of water cannot be eliminated. I have several times seen the onset of decompensation with uremia accompany the oliguria of an intercurrent febrile complication, here, presumably, the increased metabolism with resultant rise in the catabolites to be eliminated also played a part.

The concepts of compensated and decompensated renal hypofunction are of fundamental significance for the interpretation of tests of renal function.

Compensated Renal Hypofunction—In this stage the concentrating power of the kidney is impaired, but this is compensated for by an increase in the volume of urine, so that there is no retention and the blood chemistry is normal. In fully compensated renal hypofunction the functional tests that are based on measuring the quantity of some substance eliminated in a given time (e. g., the phenolsulphonphthalein test) give a normal result if sufficient water is available, the test substance is excreted by means of a polyuria in the usual time though in lesser concentration. In order to detect compensated renal hypofunction, it is necessary to determine the maximum concentration of the urine. In the calculation of the Ambard constant, the concentration of

urea in the urine is considered, but this concentration is a random one and not necessarily the maximum. Moreover, Maclean²⁰ has pointed out that the arrangement of the formula is such that variations in the urinary concentration play only a relatively small rôle in comparison to changes in the blood urea. Maclean's urea concentration test reveals admirably the presence of renal hypofunction, but it involves a chemical determination in the urine. From the foregoing it is seen that we can dispense with any chemical determination, for renal hypofunction will be revealed by an abnormally low specific gravity of the urine under circumstances in which the functionally intact kidney would elaborate a urine of high specific gravity. These principles are applied in the concentration and dilution tests of Volhard,²⁹ which we have found to be the best means of detecting compensated renal hypofunction.

Volhard's technic, which we followed originally, consists in having the patient empty his bladder on rising in the morning and then drinking 1,500 cc of water (we have found 1,200 cc ample) within a half-hour. For the rest of the day the patient takes only dry food. The patient voids every hour in the morning and every two hours in the afternoon and the volume and specific gravity of the individual specimens are recorded. The normal patient voids the ingested water within four hours and his urine attains a specific gravity of from 1.028 to 1.034 late in the afternoon or early evening.

We have found that attempts to carry out both the concentration and dilution tests in the same day often lead to failure to attain the maximum specific gravity of which the kidney is capable because of the delayed excretion of the ingested water. This prolongation of water elimination may be due to myocardial insufficiency or be a manifestation of severe renal injury, which may protract the excretion of the water to twenty-four or more hours. To obviate this we perform the concentration test alone, in the following simple way.

The patient has his customary supper and then takes no fluids till four hours after waking the next morning. On waking, he empties his bladder, this urine is discarded. He voids hourly for three hours and the specific gravity and volume of each specimen is recorded. Should he be unable to pass urine each hour, one is omitted, so that there are only two specimens. It is best that the patient remain in bed during these hours. The highest specific gravity of the three specimens is considered as representing his maximum concentrating capacity. In health the specific gravity reaches from 1.026 to 1.034, usually about 1.030. We have not seen true uremia in any case in which the maximum specific gravity reached 1.020 or over. A maximum specific gravity under 1.020 indicates impaired renal function. In the severest

29 Volhard (Footnote 5, p. 1198)

cases the patient is unable to concentrate above 1 010. Small amounts of albumin do not notably affect the result. In evaluating the results one must always be sure that edema or a serous effusion is not being evacuated, for this may simulate inability to concentrate.

Decompensated Renal Hypofunction—In the decompensated stage of renal hypofunction, the loss of concentrating power is not balanced by an increased urinary volume, and retention of the substances that are normally highly concentrated by the kidneys occurs. To demonstrate the existence of the decompensated stage, therefore, it is necessary to find retention of urinary constituents in the blood, though the presence of renal decompensation may be surmised from the combination of a low maximal specific gravity of the urine with oliguria or a very low phenolsulphonphthalein output. Either the urea or the nonprotein nitrogen concentration of the blood may be used as an indicator of the onset of decompensation. Theoretically, the determination of urea is preferable to that of nonprotein nitrogen because the urea concentration in the blood is approximately equal to that in the tissues,³⁰ even in the most marked retention,³¹ while the nonprotein nitrogen content of the tissues is much greater than that of the blood. We have not found that uric acid and creatinine determinations, which are much more liable to error than the estimation of urea, yield any diagnostic or prognostic information not afforded by the urea concentration.

PRERENAL DEVIATION

When renal function is impaired the power of the kidney to eliminate water, as judged by the Volhard water test, often remains surprisingly good for a considerable time, but ultimately becomes impaired, and in addition to inability to concentrate the patient can no longer elaborate a very dilute urine. In such cases the defective water elimination, if not cardiac, is merely part of the impaired renal function which affects the excretion of all the urinary constituents.

Much more common than defective water excretion as a manifestation of impaired renal function is failure of water excretion due to extrarenal causes. Such cases are recognized by the unimpaired concentrating power of the kidney revealed by the high specific gravity of the urine. As stated above, there is little sodium chloride in the urine, but this in itself does not suffice to depress the specific gravity markedly. If such a patient drinks 1,500 cc of water only a small portion is eliminated within four hours. The rest "leaks away" into the tissues, lowering the water content of the blood close to the water threshold, this prevents

30 Marshall and Davis. Urea. Its Distribution in and Elimination from the Body, *J Biol Chem* 18 53, 1914.

31 Weiss and Vaughn. Chronic Nephritis with an Unusual Degree of Nitrogen Retention, *J Lab & Clin Med* 7 229, 1921.

the copious diuresis that normally follows the drinking of so much water. This abstraction of fluid from the blood may aptly be termed prerenal deviation. It is encountered in such varied conditions as nephrosis, certain cases of glomerulonephritis, myocardial failure, high intestinal obstruction and profuse diarrhea. The urine in prerenal deviation is reduced in volume, of high specific gravity, with a high concentration of urea but a low concentration of chloride. The blood urea may rise to great heights if there is marked oliguria while the chloride content may be very low if the fluid lost contains much chloride. The relations between compensated and decompensated renal hypofunction and prerenal deviation are summarized in table 3.

TABLE 3—*Relation of Compensated and Decompensated Renal Hypofunction and Prerenal Deviation*

	Concentrating Power	Diluting Power	Blood Urea
Compensated renal hypofunction	Impaired	Normal	Normal
Decompensated renal hypofunction (renal insufficiency)	Impaired	Normal or impaired	Elevated
Prerenal deviation	Normal	Impaired	Normal or elevated

SUMMARY

1 Impairment of renal function involves all the excretory functions of the kidney.

2 No matter what the anatomic substratum—arteriosclerotic or inflammatory change, polycystic transformation or prostatic obstruction—impairment of renal function is always manifested in the same way, namely, by a lowering of the maximum concentration in which each of the individual urinary constituents can be excreted.

3 As impairment of renal function progresses, the maximum specific gravity attainable falls correspondingly. But no matter how severe the injury to renal function, the maximum specific gravity attainable does not fall below 1.010.

4 When selective retention occurs in Bright's disease, it is not due to inability of the kidney to excrete the retained substance but to the intervention of an extrarenal factor.

5 The primary criterion whether or not a substance rises in concentration in the blood as a result of renal insufficiency is the normal value of the ratio $\frac{\text{average concentration in urine}}{\text{concentration in blood}}$ for that substance. If this ratio is high (e. g., urea) the substance will accumulate in the blood in renal insufficiency, while if the ratio is low (e. g., chloride) it will not.

6 Fully compensated renal hypofunction is revealed only by a lowered maximum concentration of the urine, for the detection of which a modification of Volhard's specific gravity test is used.

Book Reviews

GASTRIC FUNCTION IN HEALTH AND DISEASE By JOHN A RYLE, M D, F R C P, Assistant Physician and Lecturer on Medical Pathology, Guy's Hospital, London Pp 152 Oxford Medical Publications, 1926

In this short monograph the author first considers the sensory, motor and secretory functions of the stomach in health. The normal gastric sensations are described and explained. The variations in gastric secretion are considered as expressions of variations in tonus, peristalsis and motility. In health they may range from complete "achlorhydria" to extreme "hyperchlorhydria." A correlation is found between the physical type of the subject and the type of gastric response, both motor and secretory. An entire chapter is devoted to the function and control of the pylorus and to the control of gastric acidity. In gastric disease, the painful sensations are ascribed to an increase of tension in the muscle fiber and the suggestion is made that nausea and anorexia are associated with abnormal relaxation. A classification of the common dyspepsias is given and discussed. One chapter is devoted to gastrojejunostomy and its sequelae.

The fractional test meal is accorded more value than seems justifiable on the basis of the data given. The author endeavors to show that all gastric distress is due to variations in the tension of the gastric musculature, and that such distress may be induced reflexly by extragastric lesions as well as by local gastric disease. The evidence presented is entirely insufficient and the view taken serves only to make the subject of abdominal symptomatology more difficult. The portion devoted to the dyspepsias has little interest. In the chapter on gastrojejunostomy, the conclusion is reached that "the most important contraindications to gastrojejunostomy are a short history, a well marked hypertonus, a high abrupt curve of acidity, and rapid emptying. The most reasonable indications for operation apart from obvious stenosis are a long history, a subnormal tonus, a slowly climbing curve, and slow emptying."

On the whole, the book is not very practical, it adds further confusion to the subject of gastro-intestinal physiology and symptomatology.

IMMUNOCHEMICAL STUDIES By CARL H BROWNING, WITH M KOSAKAI, T J MACKIE, T TANIGUCHI, G H WILSON, N YOSHINARE. Pp 239 Price, \$4.50 New York William Wood & Co, 1925

It would be refreshing to read a treatise on the topic designated by the title in which the discussions are made in a relatively simple and clear manner, and without reference to the befuddling terminology existent in the field of immunology during the last twenty years. Such desired clarity is not contained in this volume, in fact, a survey of the literature references quoted demonstrates that most of the text could have been written as well ten years or more ago as in 1925. If an attempt was made to add new facts or ideas in the field of immunology the effort was futile.

SCOLIOSIS By SAMUEL KLEINBERG Pp 291 Price, \$6 New York Paul B Hoeber

This is an excellent and comprehensive treatise on scoliosis. It places special emphasis on the abandonment in the severe cases of the time honored exercises, braces and casts. The correction of the deformity, so far as possible, is accomplished by plaster jackets applied by the Abbott method or by the Kleinberg method, followed by his ingenious and satisfactory brace. When the maximum correction has been attained, a fusion operation, which is in

effect a combination of the Hibbs operation and a bone splint, is then performed. It is somewhat surprising to note Kleinberg's advocacy of beef bone splints, in view of the fact that most operators have abandoned the use of beef bone except in the form of screws or intramedullary pegs. The book is a definite step forward in the elimination of much that is, or should be, obsolete in the treatment of this distressing deformity. The views on operative treatment, while somewhat advanced, will undoubtedly find wide acceptance among the modern practitioners of orthopedic surgery.

NEPHRITIS By DR. HIRSHMAN ELWYN Price, \$5 New York Macmillan Company

This book is largely a compilation, but in the assembling of facts and theories Dr. Elwyn has shown an unusual amount of wisdom. He has exercised editorial discretion as to what to include and what to omit. The result is a well considered, comprehensive resume of the essentials of present day knowledge of nephritis. The author has injected his own personality into the book. His views are never in doubt, but they are not offensively obtruded. Moreover, they are clearly the result of wide reading, close observation at the bedside, and intimate familiarity with the laboratory. But all the knowledge contained in the volume, and all the wisdom manifested in working over that knowledge might have been largely wasted had there been lacking skill in presentation. Fortunately there is no such lack. The author has the gift of style. He knows how to condense, how to write simply yet with scientific accuracy, how to present a subject in an orderly manner. He writes attractively, forcefully and clearly.

The work includes a brief review of the anatomy and physiology of the kidney, a discussion of renal insufficiency, hypertension and uremia. The various classifications of nephritis are reviewed and that of Volhard and Fahr rather closely followed. The etiologic, pathologic and clinical features of the various types of nephritis are then considered with sufficient but not bewildering detail, due to attention being given to treatment.

The book is written from the modern point of view of nephritis. The practitioner who has had difficulty in keeping up with the recent advances and who may be bewildered by references in the literature to arteriosclerosis, nephrosis, Mosenthal meals, nonprotein nitrogen of the blood, etc., will find the book helpful. To him as to the medical student it may be heartily recommended.

A MANUAL OF CLINICAL LABORATORY METHODS By C. L. CUMMER, PH. B., M. D.
Second edition, revised Pp 547, 181 illustrations Price, \$6.50 Philadelphia Lea and Febiger, 1926

The first edition of this manual contained concise instructions for making any of the usual simple and the more complicated clinical laboratory examinations. To these are added in this new edition certain revisions, notably in the chapter dealing with the Wassermann reaction. Other changes are made in the directions for the chemical examinations of the blood. A section on cutaneous reactions and a chapter on basal metabolism are new features.

As a text for medical students and a guide for physicians and laboratory technicians, this book is recommended without reserve and is adequate in every respect.

PSYCHOANALYSIS AND BLIND PSYCHOANALYSIS By LEONARD L. LANDIS, M. D.,
140 East Twenty-Second Street, New York

There is no merit in this book either from the standpoint of the medical man or of the lay public. It is stamped by the author's picture and by the introduction, the two, fortunately coming at the beginning of the book, should be words to the wise. There are statements made throughout the book that either fail in sense or are unfortunate interpretations of the work of other men.

DEVELOPMENT OF OUR KNOWLEDGE OF TUBERCULOSIS By LAWRENCE F FLICK, MD, LL D, Cofounder of the Rush Hospital for Diseases of the Chest, Cofounder of the Henry Phipps Institute Pp 783 Price, \$7 50 Lancaster, Pa Press of Wickersham Printing Company, 1925

This is a well written erudite exposition of the history of the steps in our knowledge of tuberculosis and its problems from early times to the beginning of this century Some evidence is produced to the effect that references to this disease were made in the Code of Hammurabi, written 2,250 years before the Christian era, and later in the Hearst medical papyrus, dating back to about the ninth year of Amenophis I, about 2,000 years before the Christian era These references are implied but the story becomes more complete and more definite in the Hippocratic writings From this point on the sequence is unbroken and each step is carefully considered It represents an exhaustive study of the literature, both ancient and modern, it shows that what has been learned has been the result of observation and study by many students from generation to generation—a countless number of workers and contributors who have added to, confirmed or corrected the theories and facts of those who have preceded them Our knowledge of tuberculosis is the sum of centuries of individual effort and team work

This volume will be of exceptional interest to phthisiologists and to medical historians but should also be of value and inspiration to all students and practitioners of medicine

LA ARTERITIS PULMONAR, CARDIACOS NEGROS By F C ARRILLAGA Buenos Aires Pedro Garcia

This is an excellent monograph of 375 pages It is profusely illustrated with photomicrographs, roentgenograms and drawings, several of which are in color It represents a study of twenty-two cases of so-called "black cardiacs" Arrillaga's work puts this subject on a firm basis as a definite clinical entity The patients are mostly old cardiac patients with histories of chronic arterial disease They generally come to the hospital with a decompensation Mitral stenosis occupies a prominent place in the etiology, being present in about one third of the cases The clinical picture is most striking In addition to the general cyanosis there is an extreme lividity of the hands, feet and head, the latter being a dark blue or even black Dyspnea, tachycardia cough and expectoration are marked The urine is generally full of albumin The blood picture is striking The leukocyte count is normal in number and kind There is, however, in every case a marked polycythemia, the red cells varying between five and a half and nine million The clinical course is rapidly progressive and death usually ensues in a few months

A complete study of the necropsy material on these cases has yielded definite results There is an inflammation and intimal thickening of the pulmonary arteries Aneurysm is common but the disease is most marked in the smaller branches in which there are invariably advanced stages of obliterating endarteritis These are constant findings and are all beautifully illustrated in the monograph

On the whole the author is to be congratulated on a brilliant piece of work

THE OCCURRENCE OF BENIGN GLYCOSURIA IN DIABETIC FAMILIES[†]

J. E. HOLST, M.D.

COPENHAGEN, DENMARK

In later years investigations into heredity have steadily assumed a greater importance in medical research. The application of the results obtained by experimental work to the study of human disease entails, however, considerable difficulty. Agreement has not yet been reached regarding the question of heredity in diabetes mellitus. One view, held by Meulengracht¹ for one, is that the disease is dependent on a single dominant factor. Against this, Hansen² has asserted that it must be assumed that the disease is caused by several factors with a similar effect. He says, "The normal development of the pancreas is determined by several factors acting in a similar way. The severe cases of diabetes occur when many factors are lacking, the mild cases, when a few are lacking." Hansen³ also expresses himself in favor of the view that there is a relation between diabetes mellitus and at least some of the mild glycosurias so commonly recognized in recent years by saying that "unser Wissen über die leichten Glycosurien in keinem Punkte dagegen spricht, dass sie alle—vielleicht mit Ausnahme der ganz vorübergehenden Fälle—auf einem geringen somatischen oder funktionellen Defekt in den Langerhansschen Inseln beruhen."

Investigations into heredity in diabetes are in certain respects attended by favorable circumstances, since the disease is common in almost every country, so that there will rarely be a lack of material that can form the basis of further investigations. In other respects we meet with a number of difficulties, some of which are common to all investigations into heredity, and others that especially apply to diabetes. The latter are connected particularly with establishing the diagnosis.

[†] Contribution from the Medical Department B of the Rigshospital, University of Copenhagen (chief physician Prof. Knud Faber).

* Given in an abbreviated form at Twelfth Scandinavian Congress for Internal Medicine, Stockholm, 1925.

1. Meulengracht, E. *Ugeskr. f. Læger* **86**: 1 (June 3) 1925.

2. Hansen, Søren. *Ugeskr. f. Læger* **86**: 341 (April 17) 1924.

3. Hansen, Søren. *Acta med. Scandinav.* **62**: 85, 1925.

In a large number of cases the disease is latent Joslin⁴ states that among his male patients above the age of 10, it was discovered by chance at an examination for life insurance in 11 per cent Among forty-eight cases of diabetes discovered fortuitously I⁵ found that in 77 per cent no diabetic symptoms of any kind were present at the time Cases of this nature will easily escape detection, and if it is a question of persons belonging to an earlier generation one will be practically entirely prevented from acquiring any information about them

Frequently the only thing known about one or more members of the family investigated is the bare fact that glycosuria is present In such cases there is great uncertainty The work of recent years has clearly shown the extraordinarily common occurrence of glycosuria whose relation to diabetes mellitus is either highly improbable (e g, the "sweet soup" glycosuria described by me⁶) or at any rate doubtful

Not uncommonly glycosuria is referred to as "sugar disease" In criticizing this we must take into consideration the fact that prior to the last few decades all spontaneous glycosuria, if it was not purely transient, was on the whole regarded as identical with diabetes mellitus, a view that cannot be endorsed now It is true that some authors distinguish between the terms glycosuria and diabetes mellitus, but often the criteria for deciding whether a case shall be included in the one or the other group is not given If one wants to be sure about these cases, therefore, it is necessary to select those in which the reason for the diagnosis is given Three points especially come up for consideration (1) the presence of the classical diabetes symptoms, (2) blood sugar determinations, and (3) the fatal course of the disease

With regard to the first factor it must, however, be pointed out that there are already a number of reports in the literature⁷ and one by me⁵ of the occurrence of symptoms in glycosuria which cannot be regarded as definitely signifying diabetes mellitus Thus, although in most cases the presence of these symptoms can be advanced as a good argument in favor of the diabetic nature of the glycosuria, they cannot constitute a certain proof in any particular case

The blood sugar estimations are more reliable In many cases these will not have been done because the routine investigation of the blood sugar has only become an established part of diabetic treatment in the

4 Joslin, E P The Treatment of Diabetes Mellitus, 1917

5 Holst, J E Undersøgelser over lette Glykosurier, thesis, Copenhagen, 1924

6 Holst, J E Ugeskr f Læger 84 224 (Feb 16) 1922

7 Roliv and Oppermann Biochem Ztschr 48 200, 1913 Salomon, H Deutsche med Wchnschr 40 217 (Jan 29) 1914 Strouse, Solomon Arch Int Med 26 751 (Dec) 1920 Allen, F M Wishart, Mary B, and Smith, L M Arch Int Med 24 523 (Nov) 1919 Motzfeldt, Ketil Acta med Scandinav 57 10 (Nov) 1922 Hatlehol, Rolf Blood Sugar Studies, Acta med Scandinav, 1924 Supplement VIII

last ten years. But even if such examinations are available the difficulties have not been disposed of, for opinion is divided as to how diabetes mellitus can be distinguished from nondiabetic glycosuria with their help. Salomon⁸ and Rosenfeld⁹ include some cases of hyperglycemia under the heading "diabetes innocens," while others do not regard the presence of normal fasting blood sugar as incompatible with diabetes mellitus.

The fatal course of the disease which affords a good basis for diagnosis is not always accessible as a not inconsiderable number of cases are recorded under other causes of death, such as gangrene and embolism.

Great difficulties are encountered through the usual lateness of occurrence of the disease. This assumes importance not only because some of the members of the family have died at an early age or, if they are still alive, have not yet reached the age when the disease most frequently appears, so that the possibility of a later occurrence cannot be passed over, but also because so many first get the disease at an age when the benign and therefore often undetected or wrongly diagnosed course is particularly frequent.

Even if the presence of typical diabetes mellitus is proved by the demonstration of glycosuria and the classical diabetes symptoms as well as the blood sugar determinations, we must convince ourselves that the cases included in this category cannot be regarded as forming an entity. Ever since von Mehring and Minkowski's¹⁰ investigations it has been known that typical diabetes mellitus can be produced by removing or destroying a sufficiently large portion of the pancreas, just as there are many examples of diabetes occurring as the result of acute pancreatitis. Diabetes is thus not necessarily caused by special constitutional factors but may be of purely exogenous origin. We cannot exclude the possibility of such an exogenous origin in some of the cases of diabetes mellitus occurring as a result of chronic pancreatitis, arteriosclerosis with degenerative changes in the pancreas or other pathologic conditions.

In this connection it may be stressed that in the last few years since introduction of the insulin treatment cases of diabetes refractory to insulin have been reported by many authors, among them Strauss¹¹ and Umber and Rosenberg¹². Among these, in addition to renal glycosuria, a number of cases of hyperglycemic glycosuria also occur, and these cases are interpreted by several authors as being of extra-insular origin.

8 Salomon (footnote 7, second reference)

9 Rosenfeld, Georg. *Berl klin Wchnschr* **53** 1093 (Oct 2) 1916

10 Von Mehring and Minkowski. *Arch f exper Pathol u Pharmakol* **26** 371, 1889

11 Strauss, H. *Klin Wchnschr* **4** 491 (March 12) 1925

12 Umber and Rosenberg. *Klin Wchnschr*, 1925, p 583

At any rate, in some of these it must be pointed out, however that the facts furnished are not so convincing that the authors' conclusions can be accepted as sufficiently well founded, but the possibility cannot be excluded that such cases of extra-insular diabetes may occur, even though, like the exogenous cases, they are only thought to constitute a small proportion of the total number of diabetes cases

In view of the occurrence of such diabetes cases one should be careful not to draw any too certain conclusions from the scanty observations concerning the descendants of diabetic parents. What usually happens is that reliable information about some of the members of the family is forthcoming, while there are only scanty details about the others. When this is the case it must be realized that we cannot count on all the cases of glycosuria in a family being of the same kind. As time goes on, the reports of cases of benign glycosuria in diabetic families are getting more numerous. The oldest case, presumably, is that of Garrod¹³ in 1913. He described a case of glycosuria in a girl of 10. It had lasted for two years, gave no subjective symptoms, was fairly independent of the diet and was associated with normal fasting blood sugar. The patient's brother, who was two years old, had typical diabetes mellitus with a considerable amount of hyperglycemia.

In 1914 the subject was discussed by Salomon,⁸ who says "Es ist oft in der Ascendens des Diabetes innocens und renalis echter Diabetes zu vermerken." Other cases have been reported by Rosenfeld,⁹ Johnson,¹⁴ Hagedorn¹⁵ and Hansen.³

Nothing definite can be said about the different cases reported by Begtrup,¹⁶ Host¹⁷ and others, since the diagnosis of diabetes mellitus cannot be regarded as having been established in these cases.

Quite recently Hatlehol¹⁸ has discussed a number of cases. Among twelve families in which benign glycosuria occurred, diabetes mellitus also was present in five. The cases of glycosuria that occurred together with diabetes were partly cyclic renal and partly the so-called transition cases. In one family the father had diabetes mellitus while one child had a transition case and another a case of cyclic renal glycosuria.

Brugsch¹⁹ also asserts that he observed diabetes and benign glycosuria in the same families. He says "Weiter ist in vielen Fällen des Diabetes innocens eine hereditär—familiäre Bindung mit dem echten Diabetes im Erbwege vorhanden. Man sieht also, auch der Diabetes

13 Garrod, A. E. Brit. M. J., 1913, p. 850.

14 Johnson, A. Acta med. Scandinav. 56:485, 1922.

15 Hagedorn, H. C. Undersøgelser vedrørende Blodsukkerregulationen hos Mennesket, thesis, Copenhagen, 1921.

16 Begtrup, E. Ugeskr. f. Læger 78:857 (May 25) 1916.

17 Host, H. F. Meddelelse i det medic. Selskab i Kristiania, Sept. 26, 1923.

18 Hatlehol (footnote 7, sixth reference).

19 Brugsch, Theodor. Ztschr. f. ärztl. Fortbildung, 1924.

innocens its ein Stuck vom Diabetes mellitus" Last, Reiter²⁰ describes the occurrence of diabetes in association with cyclic hyperglycemia as well as with transition cases

With regard to these earlier cases, however, it must be remarked that some of the authors themselves interpret them in another way than that given here, for instance, Salomon⁸ and Rosenfeld⁹ refer some cases of hyperglycemia to diabetes innocens

Finally, I have myself observed diabetes mellitus and benign glycosuria in the same family a number of times. These cases are briefly reported below in connection with the genealogic trees. With respect to the diagnoses it should be stated that by diabetes mellitus is understood cases with fasting hyperglycemia while the term nondiabetic glycosuria embraces all cases of glycosuria in which the fasting blood sugar is normal without it being due to antecedent dietetic treatment

GENEALOGIC TREES

The following signs are used in the genealogic trees in the accompanying illustrations. A square figure means a male, a circle, a female. Cases of diabetes are indicated by black, benign glycosuria by Δ in the figure denoting the sex. Cases of glycosuria in which the available information is insufficient for a certain diagnosis are indicated by horizontal shading.

Unfortunately the information about the families is sometimes rather meager, for in some of the cases only facts concerning the members who had glycosuria were obtainable. The first genealogic trees are examples of the simultaneous occurrence of diabetes and nondiabetic glycosuria among brothers and sisters.

FAMILY I

CASE 1—A man, aged 42, at the age of 10 had lung disease. For some years he had had slight attacks of pain in the epigastrium, accompanied by nausea but without fever, vomiting or jaundice.

Glycosuria was demonstrated in 1907 (1 per cent) at examination for life insurance and was found several times subsequently.

In 1922 the patient was again investigated. He had not been dieted in the meantime, and did not exhibit subjective diabetic symptoms.

The fasting blood sugar was found to be normal and the urine gave a weak sugar reaction. After the administration of 68.5 Gm of glucose (1 Gm per kilogram) the fasting blood sugar rose at most to 0.166, and the rise was at an end in two hours.

CASE 2—A woman, aged 39, had been treated in the hospital two years before this illness for typical diabetes mellitus. On admission 3 per cent sugar was found in the urine and 0.3 per cent in the blood.

²⁰ Reiter, P. J. *Undersøgelser over Sukkerstofskiftet ved Psychoser*, thesis, Copenhagen, 1925.

FAMILY II TWO CHILDREN WITH GLYCOSURIA

CASE 1—A man, aged 38, had had glycosuria demonstrated in 1915 after he had felt weak for about a week, had lost weight and had had remarkably frequent and voluminous urination

During his stay in the hospital in 1915 and 1916 there was continuous, slight glycosuria, the highest being 0.8 per cent on an unrestricted diet. The blood sugar curve after administration of 50 Gm of white bread showed a normal rise.

Since 1916 glycosuria has steadily decreased and since 1921 could not be detected at all in spite of several examinations.

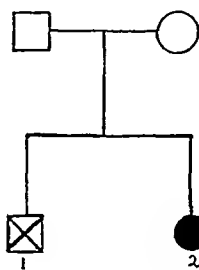


Fig 1—Families I and II

In 1923 examination was made after the administration of 50 Gm of glucose while fasting (patient's weight, 92 Kg), before the administration the blood sugar was 0.097, it rose to 0.151 and after two hours, when the test was ended, it was 0.121. Slight glycosuria occurred during the test.

For several years the patient had not been dieted.

CASE 2—The patient, a woman, died at the age of 37 in diabetic coma.

FAMILY III THREE CHILDREN WITH GLYCOSURIA

CASES 1 and 2—A boy and a girl both died at the age of 11 in diabetic coma.

CASE 3—A man, aged 24, had glycosuria demonstrated in 1913 at several examinations but it disappeared spontaneously in a short time. He had not been dieted since and exhibited no subjective typical symptoms.

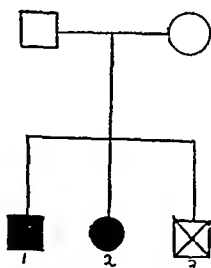


Fig 2—Family III

In 1922 examination was made after the administration of 52.5 Gm of glucose (1 Gm per kilogram) while fasting. Before administration the blood sugar was 0.086, it rose to 0.189 and after one and three fourths hours was 0.088. Slight glycosuria occurred during the test.

FAMILY IV GLYCOSURIA IN FATHER AND TWO CHILDREN

CASE 1—In this patient, a male, glycosuria was demonstrated on only one occasion.

CASE 2—The patient, a boy, died at the age of 16 in diabetic coma.

CASE 3—A man, aged 23, in 1916 had glycosuria demonstrated at repeated examinations made on account of weakness and loss in weight. During nine days' stay in the hospital shortly after, the glycosuria could not be detected. Two blood sugar examinations gave 0.116 and 0.102.

In 1925 the patient felt well and had no signs of diabetes.

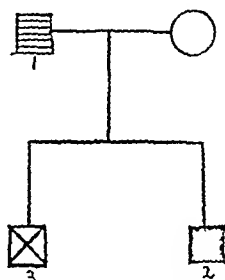


Fig 3—Family IV

FAMILY V THREE CASES OF GLYCOSURIA

CASE 1—A woman died from diabetes at the age of 70.

CASE 2—A man, aged 21, had glycosuria detected in January, 1923, at an examination on account of weakness. At frequent examinations subsequently the fasting blood sugar was always normal.

After administration of 64 Gm of glucose (1 Gm per kilogram) while fasting the blood sugar rose to 0.175 and the rise was at an end in one and one-half hours. Slight glycosuria occurred during the rise. After taking 50 Gm of white bread, the blood sugar rose to 0.135 without glycosuria.

CASE 3—A woman, aged 23, for two years had typical diabetes mellitus with fasting hyperglycemia. She is now having insulin treatment.

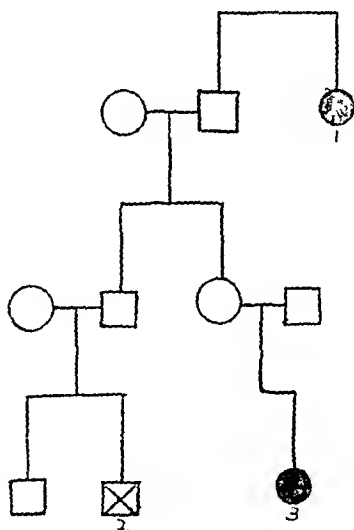


Fig 4—Family V

FAMILY VI FOUR CASES OF GLYCOSURIA

CASE 1—A male died of diabetes.

CASE 2—The patient, a man, was treated in 1915 in the hospital for "sugar disease." The urine contained only a small quantity of sugar, symptoms of mild diabetes, thirst, polyuria, etc., were present. He is now said to be healthy.

CASE 3—Glycosuria was demonstrated in the patient, a woman, in 1921. At a single examination then, 3 per cent sugar was found in the urine while numerous subsequent examinations on an unrestricted diet have always given a negative reaction.

CASE 4—A woman, aged 40, had examinations in 1907 and 1908 on account of salpingitis, the urine was found free from sugar. Glycosuria was detected in 1910 at an examination on account of thirst, lassitude and loss in weight (16 Kg in eighteen months)

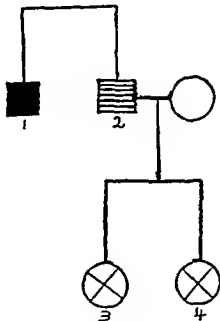


Fig 5—Family VI

On admission to the hospital the urine gave a positive reaction for sugar, acetone and diacetic acid, the patient was dull and drowsy and the condition was regarded as incipient diabetic coma. The acidosis, however, disappeared quickly, the glycosuria persisted somewhat independently of the diet.

The patient was later treated in the hospital in 1912, 1914, 1915, 1917, 1921 and 1923.

At many examinations during the last five terms of hospital treatment, a normal fasting blood sugar was always demonstrated. In 1923 examination was made after the administration of 50 Gm of glucose while fasting. Before the administration the blood sugar was 0.088, it rose to 0.195 and was again normal in two hours.

During each visit to the hospital the urine contained sugar, usually even while fasting.

At the last admission rather pronounced acidosis was found as in 1910 and, just as at that time, the patient appears to have been diagnosed as a case of threatening coma. During this visit, however, the acidosis also disappeared rapidly.

Dietetic treatment was carried out only periodically.

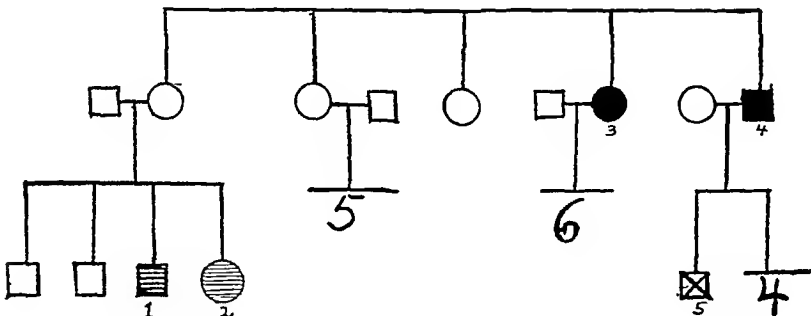


Fig 6—Family VII

FAMILY VII FIVE CASES OF GLYCOSURIA

CASE 1—A man, aged 55, for some years had glycosuria without subjective typical symptoms.

CASE 2—A woman, aged 65, had the same condition as patient 1 of this family group.

CASE 3—A woman died from diabetes at the age of 76, after thirteen years of typical illness

CASE 4—A man died from diabetes at the age of 65. He had had the disease for a year or two

CASE 5—A man, aged 45, had marked glycosuria demonstrated in April, 1922, and again in June, 1923. Two blood sugar examinations showed normal fasting blood sugar

In June, 1923, the patient was examined after the administration of 50 Gm of glucose. The blood sugar before administration was 0.093, it rose to 0.189 and was normal again in two hours. Slight glycosuria occurred during the test

In the following cases glycosuria occurs in several generations

FAMILY VIII FOUR CASES OF GLYCOSURIA

CASE 1—A woman, aged about 60, suffered from typical diabetes mellitus with considerable hyperglycemia

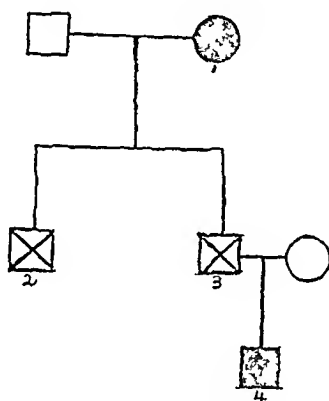


Fig 7—Family VIII

CASE 2—A man, aged 34, had glycosuria demonstrated in 1910 and several times later, the highest being 1 per cent. He had no subjective typical symptoms. The patient avoided sugar but otherwise took a normal diet

At three blood sugar examinations in 1922 normal values were found

CASE 3—A man, aged about 28, had glycosuria for four or five years without subjective symptoms. No information about blood sugar examinations was available

CASE 4—A boy died in typical coma at the age of 2

FAMILY IX FOUR CASES OF GLYCOSURIA

CASE 1—A male died of diabetes

CASES 2 and 3—Two males suffered from "sugar disease." No further details were given

CASE 4—A man, aged 30, had glycosuria demonstrated in 1915 at an examination for life insurance, and several times afterward, always a small amount. The patient avoided sugar but otherwise took a normal diet. The fasting blood sugar and the rise after the administration of glucose were normal at several examinations (after 50 Gm of glucose the highest value being 0.17). The last examination was in 1922

FAMILY X SEVEN CASES OF GLYCOSURIA

CASES 1 and 2—Two males died of diabetes

CASE 3—A girl, aged about 12, suffers from diabetes gravis but is now under insulin treatment

CASE 4—A man died at the age of 72 of cancer of the liver He had glycosuria from age of 46 but no further details about it were obtainable

CASE 5—A man, aged 60, had diabetes for twenty-five years with as much as 8 per cent sugar in the urine and considerable hyperglycemia

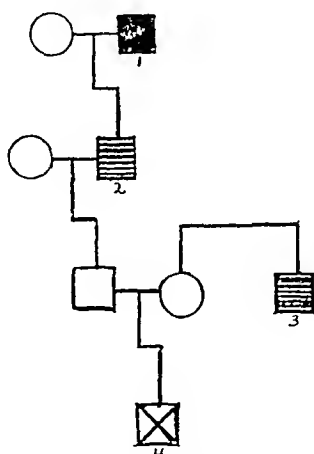


Fig 8—Family IX

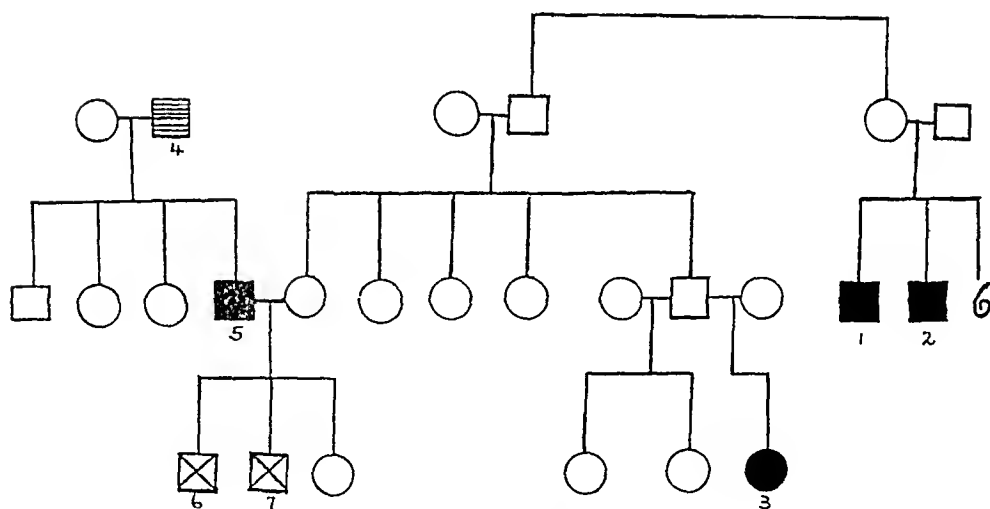


Fig 9—Family X

CASE 6—A man, aged 31, had glycosuria demonstrated in 1917 and many times after The patient avoids sugar but otherwise does not diet himself now, though earlier he did so periodically

No diabetic symptoms were noted The fasting blood sugar on repeated examinations was always normal

In 1922 a test was made after the administration of 75 Gm of glucose (1 Gm per kilogram) Before administration the blood sugar was 0.103, afterward it rose to 0.24 and was normal again in one and one-half hours At two threshold examinations sugar excretion occurred with a rise to 0.149 but not with a rise to 0.126

Another examination for glycosuria in 1923 gave practically the same result

CASE 7—A man, aged 28, was examined in December, 1924, a few days after glycosuria was demonstrated. Glucose, 71 Gm (1 Gm per kilogram), was given. Before the administration the blood sugar was 0.092, afterward it rose to 0.165 and was normal again in an hour. At the threshold determination marked sugar excretion was found with blood sugar rise to 0.145.

FAMILY XI EIGHT CASES OF GLYCOSURIA

CASE 1—A man died of diabetes at the age of 36.

CASE 2—A girl died in diabetic coma at the age of 6.

CASE 3—A woman, aged 20, had glycosuria demonstrated in 1920 in connection with diphtheria and several times afterward, always slight. She never dieted, and felt perfectly well. In 1923 examination was made after the administration of 50 Gm of glucose. Before administration the blood sugar was 0.098, afterward it rose to 0.15 and was normal again in one and three-fourths hours. There was slight excretion of sugar during the test.

CASE 4—A man, aged about 50, had glycosuria for twenty years without subjective symptoms.

CASE 5—A man, aged about 45, had glycosuria for "many years" without subjective symptoms.

CASE 6—A man, aged 47, had glycosuria from the age of 18. At that time he is said to have had from 10 to 12 per cent sugar in the urine and to be "at the point of death." He now feels perfectly well.

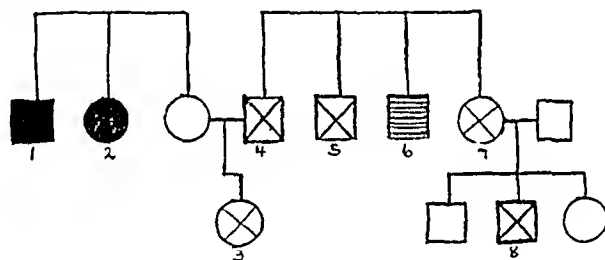


Fig 10—Family XI

CASE 7—A woman, aged about 50, had glycosuria on and off for twenty-nine years. She avoided sugar but otherwise took a normal diet. Examination of the fasting blood sugar in 1917 gave a normal result.

CASE 8—A man, aged 29, had glycosuria demonstrated in 1914. Many examinations were made in 1914, 1917, 1919, 1923 and 1924 of the fasting blood sugar and the rises after glucose administration always gave normal results. Glycosuria was often present while the patient was fasting. For several years the patient has not been dieted.

In order to give the right impression of the frequency with which orthoglycemic glycosuria and diabetes mellitus occur in company with one another, I must also state that besides the cases referred to here I have observed a considerable number of families in which the same association seems to occur. I have not included these, however, because there are so many gaps in the information and examinations that the individual cases could not be judged with the requisite accuracy.

If my observations are taken with the earlier pronouncements, especially of Salomon, Brugsch and Hatlehol, I do not believe it will be possible to look on the simultaneous occurrence of diabetes mellitus and nondiabetic glycosuria in the families as fortuitous, the frequency seems to be too great.

Like earlier authors I have found that the cases of glycosuria occurring in diabetic families do not belong to definite types but that cases due to alimentary hyperglycemia as well as renal forms and transition cases are found. In one instance I found in the father and two sons of the same family three different forms of glycosuria, diabetes mellitus, glycosuria with alimentary hyperglycemia and alimentary renal glycosuria (family X). This corresponds to a case in one of the families described by Hatlehol.

The detection of the association of diabetes and nondiabetic glycosuria is important in several different ways. From a purely practical standpoint it greatly emphasizes the necessity for blood sugar examinations as a necessary element in the investigation of a case of glycosuria even when other cases in the family provide weighty evidence for regarding it as either diabetic or innocent.

Furthermore, these observations possess great theoretical interest both for the question of heredity in diabetes and for the limitation of the term diabetes mellitus. But they can hardly be used in support of any of the views advanced concerning the heredity of the disease. As mentioned above Søren Hansen has held that the different forms of glycosuria, from the mildest to the most severe diabetes, differ only quantitatively, the mild forms depending on the absence of a few and the most severe on the absence of many of the factors concerned in the occurrence of diabetes. A sharp distinction between mild and severe diabetes cannot be drawn, however, a mild case can develop into a severe one. If, therefore, orthoglycemic glycosuria was only quantitatively different from actual diabetic glycosuria we should expect to see the development of orthoglycemic into hyperglycemic forms more frequently, for one good reason that the former have often had absolutely no treatment. But such a transition, as I have shown,⁵ occurs extremely rarely, if it can be regarded as having been definitely demonstrated at all.

If, therefore, it is contended that diabetes is caused by a plurality of factors and that at the same time there is an hereditary connection between diabetes and orthoglycemic glycosuria, it seems more reasonable to assume that there are several differently acting factors, some of which are specific for diabetes mellitus while others are common to it and orthoglycemic glycosuria. The conception, defended principally by Meulengracht that diabetes is caused by a single dominant factor is not supported by the present observations although they are not incompatible with this hypothesis. The question is hardly ready to be definitely settled, but the increasing frequency with which the association of diabetes mellitus with benign glycosuria is observed makes it worth while further to investigate this subject with more extensive material.

SUMMARY

1 In eleven families, described here, both diabetes mellitus and non-diabetic glycosuria occurred

2 The glycosuria occurring in the diabetic families was of no definite type but comprised cases due to alimentary hyperglycemia as well as the renal form

3 The association of diabetes and nondiabetic glycosuria was observed so frequently that it could not be fortuitous, but must have depended on an hereditary biologic relationship

4 The restricted extent of the material did not permit definite conclusions to be drawn concerning the nature of this relationship, but it seemed hardly likely to be due entirely to a quantitative difference

PERNICIOUS ANEMIA, ACHYLIA GASTRICA AND COMBINED CORD DEGENERATION AND THEIR RELATIONSHIP *

ROY R GRINKER, M D

CHICAGO

The first description of idiopathic anemia by Addison in 1855 and the subsequent work in 1872 by Biermer, who coined the term pernicious anemia, contained no mention of achlorhydria or combined cord degeneration. It was not until 1866 that Cahn and von Mehring¹ first discovered the absence of free hydrochloric acid in the gastric juice in a case of pernicious anemia. Since then the relationship of achlorhydria and pernicious anemia has been recognized and of late has been the subject of considerable conjecture.

I propose to consider here this association of the gastric anacidity, the cord changes and the anemia, and it is hoped that by a survey of the literature and the study of some new material that the important known facts in this relationship may be summarized.

The absence of free hydrochloric acid in the gastric contents of pernicious anemias has been reported to be 100 per cent by Ewald,² Zadek³ and Weinberg⁴ in a large series of cases. In this country Levine and Ladd⁵ at Johns Hopkins Hospital found in 150 cases only three with a normal amount of acid. At necropsy one of these cases was confirmed, the other two not certainly addisonian. Five cases with free hydrochloric acid, with a doubtful blood picture, proved to be not pernicious. Hurst and Bell⁶ in 1922 found that sixty-four of sixty-six cases had total anacidity, and in 1925 found thirty-six analyzed cases to be achlorhydric. On the other hand, MacBride and Carmichael⁷ report that fourteen cases out of fifty-five had free hydrochloric acid, four of these were examined at necropsy and the diagnosis was definitely proved.

I have analyzed the hospital histories of a series of seventy-four cases of pernicious anemia and found only three cases with free acidity.

* From Cook County and Weslev Memorial Hospitals

* Read before the Chicago Society of Internal Medicine, Jan 15, 1926

1 Cahn, A, and von Mehring, J. *Deutsches Arch f klin Med* **39** 233, 1886

2 Ewald, Kraus, and Brugsch. *Spec Path u Therap* **8** 1216, 1920

3 Zadek. *Schweiz med Wehnschr* **51** 1087, 1921

4 Weinberg. *Deutsches Arch f klin Med* **124** 447, 1918

5 Levine, S. A., and Ladd, W. S. *Bull Johns Hopkins Hosp* **22** 254 (Aug) 1921

6 Hurst, A. F., and Bell, J. R. *Brain* **45** 266 (Oct) 1922

7 MacBride and Carmichael. *Proc Roy Soc Med (Neurol Sec)*, 1925

SUMMARY OF FINDINGS

CASE 1—A man, aged 36, complained of generalized weakness and dyspnea for one year. His skin was lemon colored. The red blood cells totaled 2,016,000, the white blood cells 3,200, and hemoglobin 43 per cent. There were many megaloblasts and normoblasts and macrocytes in the blood smear. A fractional test meal revealed free hydrochloric acid 30, total 70. Roentgen-ray examination was negative. No other cause for the anemia was found.

CASE 2—A man, aged 49, complained of loss of weight and gastric distress for six months. The red blood cells totaled 3,144,000, hemoglobin 40 per cent, white blood cells 5,800, free hydrochloric acid 30, total 60. A blood smear revealed abnormally large cells. Physically and roentgenologically there was no other cause for his condition.

CASE 3—A woman, aged 42, who complained of dyspnea for two years, developed lemon colored skin and loss of weight. The blood count at entrance was red blood cells 4,500,000, hemoglobin 55 per cent, free hydrochloric acid 30, total acid 60. Nothing else was found. During two months in the hospital she developed tingling and numbness in the legs and then presented the objective neurologic signs of subacute combined cord degeneration.

It should be stated just what clinical criterion should be adopted for the diagnosis of pernicious anemia. Certainly the subjective and objective symptoms are too variable and are not specific for the disease. The blood count is often misleading, nucleated cells are inconstant, and the color index may be above or below 1 in secondary or pernicious anemia. The constant sign in Addison's anemia is the great variation in size of the red cells, yet the average size is greater than normal. Price-Jones⁸ has introduced an accurate method of charting this fact. He measures carefully 500 cells and records the number of cells of each size. He charts these on a graph, the abscissa representing the number and the ordinate the size in microns. Normal blood cells are between 4.7 and 9.5, averaging 7.2 microns. In pernicious anemia the cells vary from 3.7 to 13.9, averaging 8.3 microns. This makes a curve with a broad base and far to the right.

The achlorhydria of pernicious anemia is characterized by its completeness and invariability. It is present throughout the course of the disease and the remissions have no effect on it. The hemoglobin may return to 90 per cent but the anacidity persists. It is, in fact, present in most cases, no matter how recently the initial symptom appeared. This is contrasted with carcinoma of the stomach, in which the achlorhydria is progressive and never constantly complete. Achlorhydria may be known to be present months or even years before the recognition of the anemia. These cases are, however, not common. Faber reports anacidity preceding the anemia by ten years. Hurst has seen an interval of twelve years, Sturtevant⁹ fourteen years, and Riley¹⁰ twenty-five

8 Price-Jones, C. J. Path & Bacteriol **25** 487 (Oct) 1922

9 Sturtevant, M. Achlorhydria Preceding Pernicious Anemia, Case of More Than Fourteen Years' Duration, J. A. M. A **85**:1638 (Nov 21) 1925

10 Riley, W. H. Achlorhydria Preceding Pernicious Anemia, Correspondence, J. A. M. A **85** 1908 (Dec 12) 1925

years In 150 cases Levine and Ladd found only three in which the anacidity preceded the disease In two cases the interval was less than a year, and one of six years No other type of anemia is associated with achlorhydria, the most severe secondary anemias usually revealing normal gastric contents

It is known that even without a gastric analysis before the onset of the disease, the history often elicits the fact that gastro-intestinal symptoms have preceded the hospitalization of the patient by some months Bramwell¹¹ in 1899 found that diarrhea often preceded the anemia and thought the previous diarrhea was evidence of an intestinal infection causing the anemia In this series of cases I found that three patients had complained of gastro-intestinal symptoms all their lives In addition one man, aged 60, had gastric upsets for the forty-five years preceding, one man for nine years, one girl, aged 24, had spells of nausea for seventeen years, and one patient had distress for twelve years Thus, in seventy-four cases there were seven, or 9 per cent, with a previous history of gastro-intestinal upsets—a number much too low from which to draw conclusions Eighteen patients complained of gastro-intestinal symptoms as the initial symptom and another twenty-eight developed some type of distress during the course of the disease Twenty-three, or thirty per cent, of the patients had no subjective symptoms of this type throughout the course of the disease, although all but two of these had complete anacidity MacBride and Carmichael report that 55 per cent of their female and 74 per cent of their male cases had no gastro-intestinal symptoms prior to the onset of the disease

Hurst concludes from these uncommon cases that achlorhydria precedes the development of pernicious anemia and must, therefore, be a predisposing factor He believes that any focus of infection, such as the teeth, sinuses or tonsils, discharging into the alimentary tract may result in an intestinal infection This takes place because the antibactericidal action of the acid is lost It has been shown that concentrations of hydrochloric acid as found in the stomach during digestion are sufficient to kill cultures of streptococci The infection then results in the absorption of toxins which presumably have two components One is hemolytic and causes excessive red cell destruction and at the same time acts on the bone marrow, resulting in the formation of excessively large cells The other component is a neurotoxin and is the cause of the spinal cord degeneration It is believed that the marrow is eventually exhausted by the continual hemolysis and that immature nucleated reds are then thrown into the blood stream During remissions the bone marrow becomes rejuvenated and is able to cope with the hemolysis, the nucleated reds disappear, but the large cells

11 Bramwell Anemia and Other Disorders, New York, Macmillan Company, 1899

persist since they are a result of the ever present toxin. The remissions are supposedly due to an increase in bodily resistance to the toxin, which, however, is never complete, therefore, relapses appear.

To prove that there is present an intestinal infection Hurst had cultured the duodenal contents and finds in every case of pernicious anemia *Streptococcus longus* of the hemolytic type, while in normal persons streptococci were present in 11 per cent, but these were never hemolytic. In a later article, from 70 to 80 per cent of the anemias were positive while no streptococci were found in the controls. Vaccines of this organism were supposed to cause almost complete remissions, however, no details are given as to how the frequently found lengthy remissions are excluded.

Kopeloff's¹² work is contradictory. He finds no difference in the bacterial content of aspirated material in a large series of normal persons and of patients having definite oral infections. Streptococci were present in about the same percentage in both series. Streptococci were found as often with low as with high gastric acidity.

Persons with anacidity should be predisposed to pernicious anemias, as the largest number of such patients are persons having achylia gastrica. Martius has shown that these patients show no anatomic change in their gastric mucosa, but are suffering from a constitutional inborn defect of the secretory power of morphologically normal glands. In favor of this is its familial occurrence in persons with or without gastro-intestinal symptoms. Albu, Udamonda and Jung have found achylia in more than one member of the same family. Children as young as 4 years have been seen with this condition. Bennet and Ryle¹³ found that four out of 100 medical students had achylia. Its early appearance suggests that not only may it be familial but that it may also be congenital. Thus, Hurst explains those relatively rare cases of pernicious anemia occurring in families, believing that they are a result of familial achylia. Among others Patek¹⁴ reports five cases of pernicious anemia in one family, all without gastric symptoms. Bartlett¹⁵ has seen five cases in a family of eight, all having had bilious attacks since childhood. Levine and Ladd found nine in 150 or 6 per cent, to be familial. I am only able to find one case in the seventy-four giving a familial history.

¹² Kopeloff. Arch Neurol & Psych 8 1-93, 1922

¹³ Bennet, T. I., and Ryle, J. A. Guy's Hosp Rep 71 286 (July) 1921

¹⁴ Patek, A. J. Family Pernicious Anemia, J A M A 56 1315 (May 6) 1911

¹⁵ Bartlett, C. J. Family Pernicious Anemia, J A M A 60 177 (Jan 18) 1913

CASE 4—A woman, aged 41, had diarrhea since the age of 14 years, she had had a breakdown for seven years during which she was always exhausted. The diarrhea became severe three years before admission. There were paresthesias and numbness in her legs. The patient was very intelligent and before knowing the diagnosis stated that she feared pernicious anemia because an aunt and uncle had both died of this disease.

In some families anemia has been associated with achylia in other members. Queckenstedt, Weinberg and Hurst report such cases. I find one case suggestive of this.

CASE 5—A man, aged 52, had stomach trouble since he was a baby. He had vomiting spells for years and always had diarrhea. He stated that his two children had exactly the same gastric distress since childhood. He had the typical findings of pernicious anemia and no free hydrochloric acid.

Certainly the presence of achylia in the families of a few patients is not evidence enough to prove a causal relationship. It may be purely casual.

If the hydrochloric acid were a barrier against infection then achylia patients should be liable to any sort of infection. On going over twelve available patients with achylia, one of whom had a daughter with the same condition, I was impressed with the frequency of infections. One had gallbladder disease, four had chronic rheumatoid arthritis, and two had infections of the colon. The other five had gastrointestinal symptoms only.

The other anacidities should also be expected to predispose to anemia. Accordingly, Hurst cites two cases of alcoholic gastritis with anacidity and typical Addisonian anemia confirmed at necropsy. Wakefield described a case of carcinoma of the stomach and achlorhydria in which the necropsy revealed in addition the picture of pernicious anemia. Garvey and Stern¹⁶ have seen a similar case. The association of gastrectomy and gastro-enterostomy with the development of anemia is remarkable. Both of these operations produce essentially an achylia.¹⁷ Conybeare and Willcox have seen pernicious anemia develop after gastro-enterostomy, and Hartman¹⁸ from the Mayo clinic describes a patient who two years after a total gastrectomy developed Addisonian anemia, due, he concludes, to the postoperative achylia. Moynihan saw pernicious anemia develop three years and eight months after a gastrectomy for cancer of the stomach. However, Lewisohn and Feldman definitely mention in reporting a large experience in gastrectomies for the last five years that they have never seen anemia appear. With so few

16 Garvey, J. L., and Stern, L. D. *Am J M Sc* **168** 847 (Dec.) 1924

17 Willson, R. N. *The Spinal Cord in Pernicious Anemia*, *J A M A* **59** 767 (Sept 7) 1912

18 Hartman, H. R. *Am J M Sc* **162** 201 (Aug.) 1921

cases in the literature, postoperative anemia, as well as that occasionally developing in the course of other diseases, must be considered as a coincidental development of pernicious anemia.

As to the source of the infection, Hurst states that he has never seen a case of pernicious anemia without oral or pharyngeal sepsis, under which he includes glossitis. That the glossitis is an infection is doubtful and rarely does it appear until the onset of the disease. It has also been seen in the secondary anemia of bowel carcinoma.

MacBride and Carmichael vigorously reject the gastro-intestinal theory because 55 per cent of the females and 74 per cent of the males of their cases had no gastro-intestinal symptoms whatsoever before the anemia was definitely established. These authors have noticed that 96 per cent of the females had a myxedematous appearance and had ceased menstruating two years before the onset of the disease. This led them to consider an endocrine disturbance as the basis of the disorder. I find the average age of anemia patients coming to a hospital to be 49 years, 88 per cent appearing in or after the fourth decade of life, furthermore, the average time between the first symptom and hospitalization was two years. It is no wonder then that menstruation should have ceased at least two years before the onset and this is no evidence to regard its occurrence as an etiologic factor.

This is a summary of our knowledge regarding the relationship of anacidity to pernicious anemia. The theory that anacidity is a predisposing factor in the production of the anemia rests on slender foundation. I found one patient who had vague symptoms of weakness seven years before it became necessary for her to have medical attention. It must be remembered that pernicious anemia may exist as a disease entity long before the typical symptoms develop. When anacidity is found in such cases it should not be interpreted as an etiologic factor but as the first sign of the disease. Only a few isolated cases of achylia definitely preceding the anemia by many years can be found, and in many series, including my own, a few cases are recorded in which the anemia was accompanied by normal acidity.

Achylia patients are apparently prone to infections, particularly arthritis. But arthritis also attacks many persons with normal gastric juice. With rare exceptions anacidity and pernicious anemia are associated. An infection of a nonspecific streptococcus should take place by other routes than the intestinal tract and thus appear as the arthritides do, for example, in people with normal acidity. The large number of cases with gastric symptoms only after the onset of the anemia suggests that the anacidity is part of the disease picture of pernicious anemia. The argument that the anemia itself does not produce achlohydria because severe secondary anemias have normal acidity may be answered by the fact that a secondary anemia with as low a red count as in

pernicious anemia is an acute condition and that the patient either dies or recovers in a relatively short time, while the average addisonian anemia patient has the disease for two years even before hospitalization

Furthermore, the hypothetic streptococcus hemolytic intestinal infection must be one without pathologic changes in the intestinal tract In view of the virulent general effect of this organism, which is not a normal inhabitant of the bowel, it seems unlikely that it may exist for so long without causing local lesions It also is unlikely that a congenital predisposing factor should be present in 88 per cent of cases for more than forty years before the development of the disease

Since Lichtheim and Minnich first described subacute combined degeneration of the cord associated with pernicious anemia, the two diseases have been considered to have an intimate relationship Nonne¹⁹ at first considered the pathologic condition of the cord to be a result of the anemia, but being unable to find cord changes in the secondary anemia patients that he examined, came to the view that the anemia and cord degeneration are due to the same toxic agent Hurst²⁰ believes that pernicious anemia is due to toxic substances composed of a neurotoxin and a hemolytic toxin which vary in their relative quantities If the neurotoxin preponderates, cord degeneration is in the foreground and may develop and persist for some time before the anemia appears I found one case in which the cord degeneration apparently preceded the anemia by four years

CASE 6—A man, aged 58, had a spastic paraplegia with incontinence of urine for four years He was unsteady on his feet and complained of tingling pains in the legs During the four years he had been treated for tabes In the hospital he was lemon colored, with less than a million red blood cells and 30 per cent hemoglobin, the blood smear was typical of pernicious anemia Deep sensation and deep reflexes were absent in the legs

If the anemia never appears the hemolytic toxin is supposedly in abeyance but is always potentially present If anemia develops during the disease it is always primary and, according to Hurst, some cases are diagnosed as secondary because the size of the red cells has not been observed Bramwell believes that the severe anemia may appear suddenly a short time before death in cases that before had a normal blood picture He finds that the blood change produces a quick reversal from spastic to flaccid paralysis Hamilton reports a case in which a remission was accompanied by the entire disappearance of objective sensory changes, which returned shortly before death Usually the remissions have no effect on the nervous symptoms In my series there is not one example of such improvement

19 Nonne *Deutsche Ztschr f Nerven* 6 313, 1895
20 Hurst *Brain* 48 155, 1925

Hurst has found in sixteen cases of cord degeneration achlohydria in 100 per cent. Vanderhof²¹ found twenty-nine cases with anacidity. However, the cases of both authors were probably associated with pernicious anemia, and are not conclusive evidence that combined cord degeneration of any etiology is associated with anacidity. Hurst states that in three cases in which the tentative diagnosis of posterolateral sclerosis was made and free acid was found in the stomach, later developments proved the patients to be syphilitic.

The argument has been advanced that the familial combined cord degeneration, which is a rare occurrence, like the familial pernicious anemia is a result of familial achylia. But Oppenheim²² has pointed out that these cases are in reality familial pyramidal degeneration, an altogether different disease and definitely hereditary.

The percentage of anemia patients developing cord degeneration has been variously stated. Dana²³ puts the number at 10 per cent, Taylor, 12 per cent, Bramwell,²⁴ 2 per cent, Nonne, 2 per cent, McCrae,²⁵ 25 per cent, Hannenbeig, 50 per cent, Hurst, 70 per cent, and Woltman²⁶ finds indisputable evidence of involvement of the nervous parenchyma in 80 per cent of these cases. What these last two observers have adopted as the clinical criterion of cord involvement is of importance. Hamilton²⁷ has clearly shown that objective and subjective neurologic signs may be present in patients who reveal post mortem no demonstrable changes in the central nervous system. These cases, however, by Marchi and Weigert stains reveal evidences of a mild peripheral neuritis which differs in no respect from that seen in other toxic conditions. It is rare to see a severe secondary anemia patient with a red blood cell count as low as the usual pernicious anemia without the presence of tingling and numbness, which usually are not associated with cord degeneration. These paresthesias caused by any type of anemia should be attributed to changes in the peripheral nerves. I therefore cannot accept, as has Woltman, that tingling and numbness are diagnostic of central nervous system involvement. Definite objective neurologic signs, such as reflex and sensory changes due to lesions of the long root fibers of the posterior columns, are used in this series as evidence of cord involvement.

On going over the seventy-four cases I find that fifty-two patients, or about 70 per cent, complained of tingling, numbness, coldness in the extremities or sensations of pins and needles. Thirty per cent had no

21 Vanderhof *Arch Clin Med* **22** 958, 1922

22 Oppenheim *Lehrbuch der Nervenkrankheiten*, Karger, Berlin, 1923

23 Dana *J Nerv & Ment Dis* **16** 205, 1891

24 Bramwell *Brit M J* **1** 1306, 1910

25 McCrae, Thomas *Pernicious Anemia*, *J A M A* **38** 148 (Jan 18) 1902

26 Woltmann, H W *Am J M Sc* **157** 400 (March) 1919

27 Hamilton and Nixon *Arch Neurol & Psychiat* **6** 1 (July) 1921

subjective sensory complaints and none of these developed combined cord degeneration. Of the fifty-two who had subjective sensory changes only twenty-four developed combined cord degeneration. My figure is therefore 30 per cent of the total.

In classifying the initial symptoms of the patients I found that diarrhea was the first sign in six cases, two of which had cord changes, pain in the abdomen in two, with no cord changes, dyspnea in seven, two of these having a pathologic condition of the cord, pallor in four cases, one having cord degeneration, loss of weight in five, with one cord degeneration, and weakness was the first symptom in twenty-six patients, of whom seven had combined cord disease. Nausea and vomiting began the picture in ten cases, with one cord degeneration. There were fourteen cases beginning with tingling, numbness and stiffness, in which all but two developed cord degeneration. Eighty per cent of the cases having paresthesias as the initial complaint developed cord degeneration, while only 20 per cent of those developing paresthesias during the course of the disease had cord degeneration.

It is seen that the most frequent symptom at the onset is generalized weakness. The high percentage of patients developing cord changes whose initial complaint was neurologic is quite striking. That this is not coincidental is borne out by the figures given by MacBride and Carmichael from a neurologic hospital in London. They found that 78 per cent of their patients with combined cord degeneration of pernicious anemia had neurologic complaints at the onset. Patients who state that their first symptom was tingling are more likely to develop posterolateral sclerosis, while if the tingling develops during the course of the anemia they are less likely to suffer from cord changes. The tingling of the latter group, I believe, is due to peripheral nerve changes and is a result of anemia, and is not restricted to any one type of anemia.

I attempted to determine if the blood count had any relation to the pathologic condition of the cord and in those cases with the full blown neurologic picture the red blood cell count was found to vary from 200,000 to 4,500,000. The lack of red cells is apparently not directly related to the cord changes.

It is well to consider what information neuropathology has to offer. Originally it was thought that there was a definite and specific localization of the pathologic condition in the posterior and lateral columns. Later investigations revealed that not only were both columns not always involved, but that the posterior or lateral may predominate in intensity, resulting in a variation of the clinical picture, and that other tracts also, such as the spinocerebellar tracts, are affected. Lesions of almost complete transverse nature have been reported. The essential pathologic condition consists of small patches of degeneration of the fibers involved. The posterior and lateral columns are often found completely degen-

erated because they are the longest in the cord and there is more chance for the resulting secondary degeneration to be summed up. The lesions consist of degenerative changes in the myelin sheaths, later axis cylinder destruction, all are accompanied by proliferation of the glial elements, which serves to remove the débris. There are never evidences of an inflammatory process. The picture has no specific characteristics and differs in no way from degeneration resulting from any toxic cause. By intrathecal stovaine injections Spielmeyer²⁸ showed that with smaller doses the posterior columns were most susceptible to changes.

If the combined cord degeneration is produced by the action of a nonspecific toxin, it should be found associated with other diseases which give rise to toxins. The literature contains quite a few such cases but with relatively few necropsies. In some the accuracy of the blood examination may be questioned. Oppenheim²² and Clarke²⁹ have seen cord degeneration on an arteriosclerotic basis, Clarke and Nonne as a result of severe secondary anemia, Schultze, Hirschfeld and Nonne report leukemic cases, Hennenberg and Oppenheim, malaria. Zadek, Redlich and Homén report eigot poisoning with the typical cord changes. Lubarsh has had a case with carcinoma and Williamson with diabetes. Marie and Zadek have noted the disease with pellagra and Mayer with lathyrism. Oppenheim has seen cases with lead, arsenic and phosphorus poisoning. Fleiner had a case with Addison's disease, and Sanders with senility. Putnam described the disease first in this country as a result of chronic ill health in women.

Hurst believes that in carcinoma of the stomach the anacidity is the main factor, and states that in the cachetic cases pernicious anemia was probably undiagnosed or that the anemia developed shortly before death.

In order to get some definite data on this subject, I have compiled cases of combined cord degeneration not associated with pernicious anemia. In three cases with the typical neurologic picture there was no anemia, but no other demonstrable etiologic factor was found, therefore, I do no more than mention them. In the following cases not only was there no Addison's anemia, but another cause was definitely proved.

CASE 7—A man, aged 62, complained of dribbling of urine and pains in the legs for a year. He had ataxia and gave a positive Romberg sign. The patellar and ankle jerks were exaggerated. The red blood cells totaled 4,000,000, hemoglobin 75 per cent, blood pressure 170 systolic, 120 diastolic. Necropsy revealed combined cord degeneration and arteriosclerosis with involvement of the vertebral vessels. The bone marrow was normal.

CASE 8—A man, aged 53, complained of abdominal pain and diarrhea. A gastro-intestinal examination was entirely negative. The deep and position senses were lost in the legs. There were ankle clonus and exaggerated reflexes. The

28 Spielmeyer *Neurol Centralbl* 69, 1909

29 Clarke *Brain* 27 29, 1904

red blood cells totaled 800,000, hemoglobin 30 per cent. The diagnosis was pernicious anemia with combined cord degeneration. Necropsy revealed carcinoma of the colon, the bone marrow was normal.

CASE 9—A man, aged 55, complained of weakness of the legs for three months. The hands and arms had little power. The skin generally was bronzed. The sensation of pain and the deep and position senses were lost in the legs. The legs were spastic with a bilateral Babinski reflex. The patient was found dead in bed one morning. Necropsy revealed tuberculosis of the suprarenals with combined cord degeneration.

CASE 10—A woman, aged 37, was unable to walk for eight weeks. She had severe diarrhea and definite mental changes. The skin showed typical pellagra skin lesions. The joint and tendon sense was absent. The ankle jerks were gone, she was ataxic and a Babinski reflex was present on one side. A definite history of dietary imbalance was obtained. She improved with a proper diet.

CASE 11—A man, aged 63, complained of incontinence. He was ataxic in the lower extremities, had increased deep reflexes, and absent tactile sensation in the legs. The blood and spinal fluid Wassermann reactions were negative. The red blood cells totaled 4,800,000, hemoglobin 80 per cent. A chest examination revealed a chronic diffuse tuberculosis.

CONCLUSIONS

- 1 Normal gastric acidity may be present in pernicious anemia.
- 2 The rarity of achylia preceding the anemia by many years makes it improbable that achylia is a predisposing cause. The fact that the anemia may go unrecognized for some time may account for these cases.
- 3 There is no evidence that there is an intestinal infection in pernicious anemia or that streptococci lying latent in the bowels of these patients are the producers of absorbable toxin.
- 4 Thirty per cent of pernicious anemia patients develop definite signs of combined cord degeneration.
- 5 Combined cord degeneration may be caused by the hypothetical toxins producing the pernicious anemia or developing during the course of the disease, but may also be the result of numerous other toxic conditions, such as Addison's disease, carcinoma of the bowel, pellagra and arteriosclerosis.
- 6 Eighty per cent of patients having paresthesia as the initial complaint developed cord degeneration, while only 20 per cent developed cord degeneration when paresthesia appeared during the course of the disease.

THE EFFECT OF ATROPINE ON GASTRIC FUNCTION IN MAN

A QUANTITATIVE STUDY *

CHESTER S KEEFER, M D

AND

ARTHUR L BLOOMFIELD, M D

BALTIMORE

The general fact that atropine may diminish gastric secretion is familiar to all physicians. In the case of animals, accurate observations are on record, but in spite of the extensive use of the drug in the clinic, no exact information is available as to the details of its action in man. The method that we have recently described¹ for estimating simultaneously the quantity of gastric secretion and discharge lends itself well to the study of this problem and this article deals with the alterations in gastric activity produced in man by administration of atropine. The study is essentially a pharmacologic one, and no attempt will be made to judge the therapeutic value of the drug in clinical disorders of the stomach.

LITERATURE

Keeton, Koch and Luckhardt² studied the action of atropine in dogs provided with Pawlow pouches. It was found that large doses of the drug abolished the secretion resulting from food stimulation. The quantity of the secretion and the pepsin concentration were diminished before there was any great alteration in the concentration of acid, this was shown best with relatively small doses of atropine. Injections of gastrin and histamine, on the other hand, if large enough, were followed by reappearance of considerable secretion even after complete temporary inhibition by atropine.

On the clinical side the literature deals largely with special pleading for or against the use of atropine in gastric ulcer, hypersecretion, pylorospasm and other conditions, and one finds few detailed studies of the objective effects of the drug. Riegel,³ a good many years ago, showed

* From the medical clinic of the Johns Hopkins University and Hospital.

1 Bloomfield, A. L., and Keefer, C. S. A Method for the Continuous Estimation of Gastric Secretion and Discharge in Man, *Arch Int Med* **37** 819 (June) 1926. The formula on page 822, of this article appearing in *Arch Int Med* **37** 819 (June) 1926, should be $[(\frac{y}{x}) \times A] - A = \text{maximum possible amount of juice secreted in ten minute period}$ instead of $[(\frac{y}{x}) \times A] - A = \text{maximum possible amount of juice excreted in ten minute period}$.

2 Keeton, R. W., Koch, F. C., and Luckhardt, A. B. Gastrin Studies II, Response of Stomach Mucosa to Food and Gastrin Bodies as Influenced by Atropine, *Am J Physiol* **51** 469 (April) 1920.

3 Riegel, F. Ueber medicamentöse Beeinflussung der Magensaftsecretion, *Ztschr f klin Med* **37** 381, 1899.

that following a meal of 1 liter of milk, the amount of stomach contents recovered and the acidity were less if the patient had previously received a dose of atropine. More recently, Bennett⁴ and Roberts,⁵ using the fractional gruel meal, report the same general results, although only a few cases were studied and in some of them the decrease in acidity was not marked. Crohn,⁶ on the other hand, obtained some contradictory results. In two patients with presumably normal secretion, administration of 1 mg (one-sixtieth grain) of atropine hypodermically was not followed by any demonstrable diminution of acidity when tested with the fractional gruel meal, later, one of these patients was well atropinized by mouth also without effect. In some patients with so-called hypersecretion, on the other hand, the secretion seemed to be checked to some extent although the degree of acidity was unchanged. The results as regards motility were uncertain. Finally, Lockwood and Chamberlin⁷ did the usual fractional analysis following an Ewald test meal before and after atropine. They conclude that both motor and secretory activity is depressed but add nothing essentially new to the observations of previous workers. In general the impression seems to prevail that atropine may lessen the normal tonus of the stomach and may abolish abnormal contractions and "pylorospasm." In view of the complexity of the gastric motor mechanism, the data available are not convincing. Bastedo⁸ concludes that in the doses usually employed, atropine is wholly without effect on the motor and secretory function of the stomach.

METHODS

The procedure employed in the present work consisted of studying the response of the stomach to a standard stimulus before and after the administration of atropine. As a rule a single hypodermic injection of 2 mg (one-thirtieth grain) was given, this dose was usually sufficient to produce distinct minor toxic symptoms—tachycardia, dryness of the mouth, blurring of vision, and unpleasant sensations of fulness in the head. The subjects were ward patients, for the most part without digestive symptoms. The test stimulus of 50 cc of 7 per cent alcohol solution was employed exactly as described in the previous article.¹

4 Bennett, T. I. Effect of Belladonna in Hyperchlorhydria, *Guy's Hosp Rep* **71** 54, 1921.

5 Roberts, R. D. Effect of Belladonna in Hyperchlorhydria, *Guy's Hosp Rep* **71** 446 (Oct) 1921.

6 Crohn, B. B. Studies in Fractional Estimation of Gastric Contents II, Effects of Antacid Medication on Gastric Acidity and Secretion, *Am J M Sc* **155** 801 (June) 1918.

7 Lockwood, B. C., and Chamberlin, H. G. Effect of Atropine on Gastric Function, as Measured by Fractional Analysis, *Arch Int Med* **30** 806 (Dec) 1922.

8 Bastedo, W. A. Points in Pharmacology of Certain Drugs Used for Stomach Effects, *Am J M Sc* **159** 53 (Jan) 1920.

RESULTS

CASE 1—A J, a man, aged 56, who entered the hospital for a minor complaint, had marked evidence of vagotonia. There was a bradycardia (pulse rate about 50 per minute) and as the control study of gastric function shows (table 1 and chart 1) he secreted large amounts of gastric juice of high acidity. When the stomach was aspirated it was noted that there were periods of excessive tonus. No essential change in the type of response was noted after the patient had taken 90 drops of tincture of belladonna for five days, except that the volume curve was markedly altered. Variations of this sort are, however, found in successive control examinations of the same person.

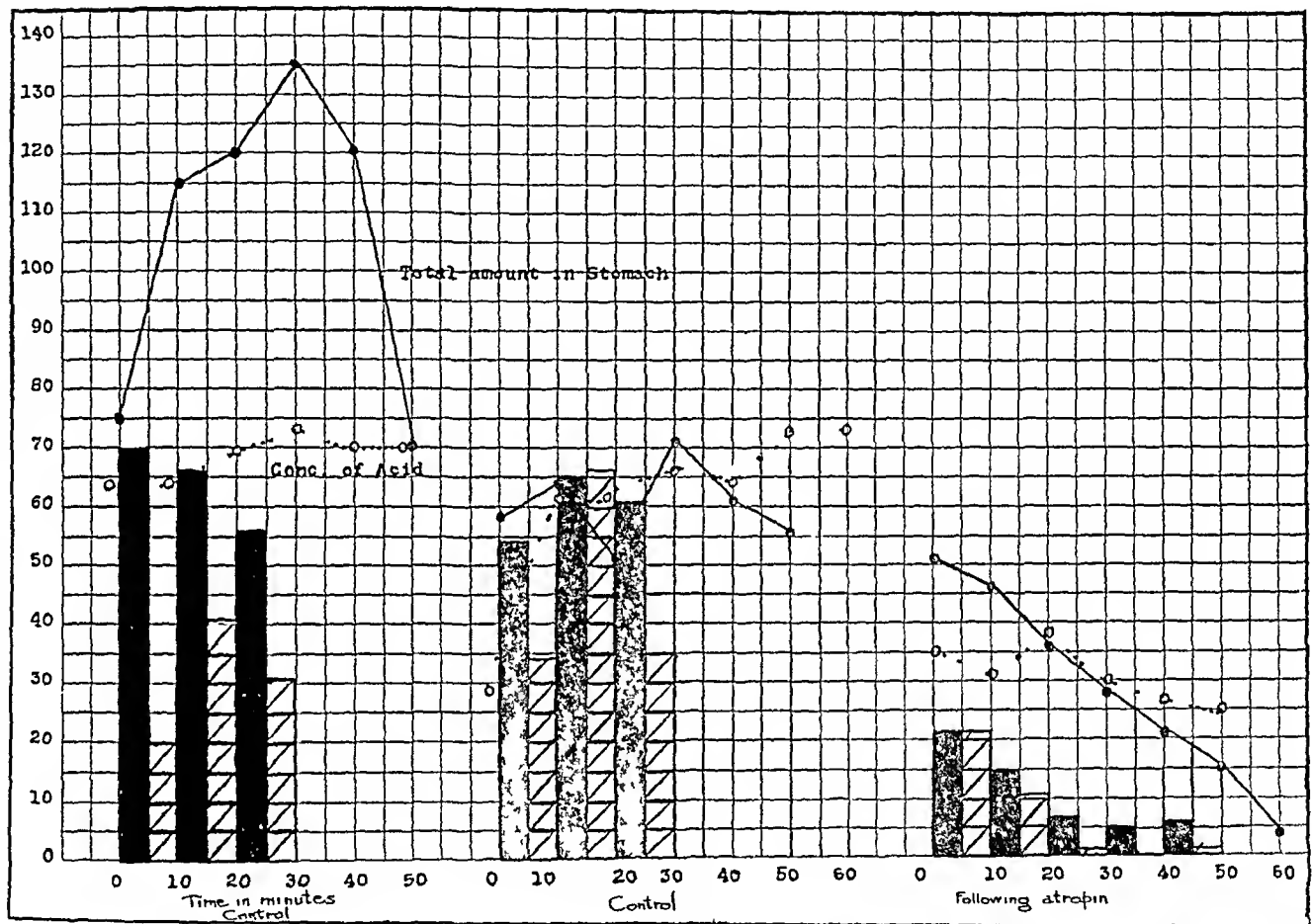


Chart 1—Observations in case 1. Solid columns indicate secretion and light columns indicate discharge (cc). The total amount in the stomach is expressed in cc and the concentration of acid in cubic centimeters of tenth normal hydrochloric acid.

After one-twentieth grain (3 mg) of atropine there was a great reduction in volume of juice secreted. In fact after the first two ten minute periods, there was almost complete cessation. The acidity of the stomach contents was reduced but less markedly than the volume. The volume curve was strikingly altered. There was a steady fall and the stomach was empty in sixty minutes, but the amount of juice discharged was much less than before atropine administration.

CASE 2—W W, a man, aged 53, had pyloric ulcer, with partial pyloric obstruction. The control examination (table 2, chart 2) showed secretion of large amounts of juice and correspondingly great discharge of fluid so that the volume of the stomach contents remained nearly constant. The patency of the pylorus was proved by regurgitation of bile. After 1/30 grain (2 mg) of

TABLE 1—Case 1

Time of Observation	Total Stomach Contents, Cc	pH	Titratable Acid Dimethyl- phenolphthalein	Volume of		Remarks
				Juice Secreted in 10 Minute Period	Volume Dis- charged in 10 Minute Period	
Without Atropin—November 25						
Immediately after test meal	75	1.7	18	22		64
10 minutes after test meal	115	1.3	40	46	20	65
20 minutes after test meal	125	1.15	52	58	41	70
30 minutes after test meal	135	1.1	64	63	31	71
40 minutes after test meal	120	1.1	64	70		71
50 minutes after test meal	70	1.1	64	70		70
After Tincture of Belladonna, 2 cc Three Times a Day for 5 Days—December 1						
Immediately after test meal	58	1.9	10	11		Pulse rate, 48
10 minutes after test meal	64	1.2	44	50	33	62
20 minutes after test meal	52	1.1	62	68	67	62
30 minutes after test meal	72	1.0	65	71	35	73
40 minutes after test meal	62	1.0	65	61		70
50 minutes after test meal	56	1.0	70	78		78
After Atropine 1/100 grain (3 mg.)—December 1						
25 minutes after injection of atropine	52	2.9	2	4		Pulse rate, 84
35 minutes after injection of atropine	46	1.9	12	14	21.5	Pulse rate, 88
45 minutes after injection of atropine	36	1.7	20	24	15.0	Pulse rate, 88, blurring of vision
55 minutes after injection of atropine	30	1.7	20	22	7.5	Pulse rate, 88
65 minutes after injection of atropine	25	1.7	20	22	5.0	Pulse rate, 84
75 minutes after injection of atropine	15	1.8	20	22	6.0	Pulse rate, 84
85 minutes after injection of atropine	4	1.9	20	22		

atropine there were no marked toxic symptoms, although the pulse rose moderately. It may be seen, however, that the volume of juice secreted was greatly reduced, 46 cc in thirty minutes as against 168 cc, whereas the degree of acidity was only slightly depressed. It is of special interest that the volume curve of stomach contents is almost identical before and after atropine although in the latter case the amount of discharge was tremendously reduced—6 cc in thirty minutes as against 136 cc.

CASE 3—W S, a man, aged 23, normal, with no digestive symptoms, had two control examinations (table 3 and chart 3) which showed essentially similar findings: secretion of abundant gastric juice of rather high acidity, with steady, fairly rapid emptying of the stomach. After atropine there was a prompt secretion of juice which was as abundant during the first ten minute period as before atropine. The secretion then rapidly diminishes and after forty minutes

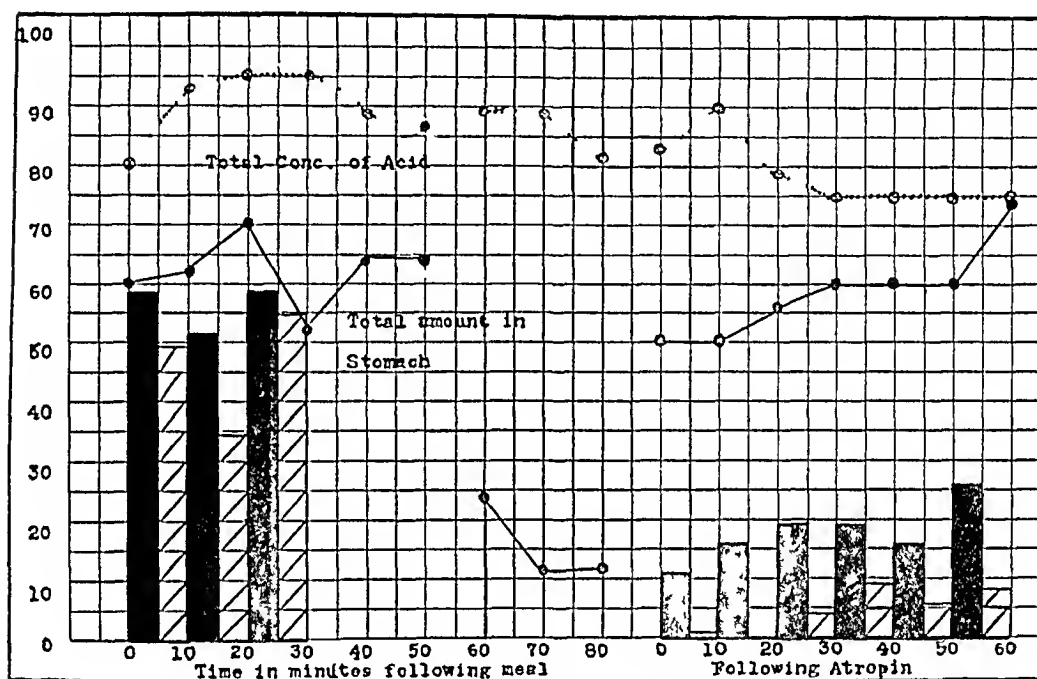


Chart 2—Observations in case 2

ceases. The acidity after atropine is much reduced even with active secretion during first period, later it is still further diminished. There is no striking change in motility.

CASE 4—W L, a man, aged 22, had a small cyst of the lung (*echinococcus*?), but was clinically well and had no digestive symptoms. The control examination (table 4 and chart 4) showed that this patient secreted rather large amounts of gastric juice of very low acidity. After atropine the pulse rate was doubled. There was a prompt response to the stomach stimulus and in the first two ten minute periods nearly as much juice was secreted as before atropine, then there was a marked decrease. The acidity of the stomach contents was practically unaffected, although it was probable that the juice secreted in small amounts toward the end of the experiment was of very low acidity. After atropine little juice passed the pylorus and the stomach emptied gradually.

CASE 5—R M, a man, aged 40, had attacks of migraine with nausea and vomiting. A control examination (table 5 and chart 5) showed steady secretion of large amounts of juice of relatively low acidity. There was a steady fall in acidity as the test progressed. After atropine the secretion was markedly and uniformly decreased. The acidity also was much diminished. The stomach emptied more quickly but much less fluid passed the pylorus.

TABLE 2—Case 2

Time of Observation	Total Stomach Contents, Gm	pH	Titratable Acid Dimethyl phenolphthalein	Volume of Juice Secreted in 10 Minute Period		Titration Period	Titratable Acidity of Pure Juice	Remarks
				Without Atropine—November 23	With Atropine			
Immediately after test meal	60	1.65	20	24			80	
10 minutes after test meal	62	1.10	64	68		47	93	
20 minutes after test meal	70	1.10	80	84	59	34	95	
30 minutes after test meal	52	1.05	84	90	52	55	95	
40 minutes after test meal	64	1.15	78	86	57		88	
50 minutes after test meal		1.15	82	86			86	Pulse rate, 68
60 minutes after test meal		1.15	88	90			90	Pulse rate, 68, slight regurgitation of bile
35 minutes after atropine	50	2.30	2		23			
45 minutes after atropine	50	1.65	32	40	12	2	90	Pulse rate, 84
55 minutes after atropine	56	1.50	40	46	16	0	77	Pulse rate, 72
65 minutes after atropine	60	1.4	50	54	18	4	75	Pulse rate, 72
75 minutes after atropine	60	1.3	50	60	19	9	75	Pulse rate, 78
85 minutes after atropine	60	1.3	60	64	16	6	75	Pulse rate, 80
95 minutes after atropine	68	1.3	66	70	26	8	75	

CASE 6—G M, a man, aged 23, who had chronic nephritis (early), had never had any gastro-intestinal symptoms. The results of examination are shown in table 6 and chart 6. It is seen that before atropine rather large amounts of juice were secreted and discharged so that the stomach was practically empty in forty minutes. After atropine, the stimulus was followed by a prompt secretion which

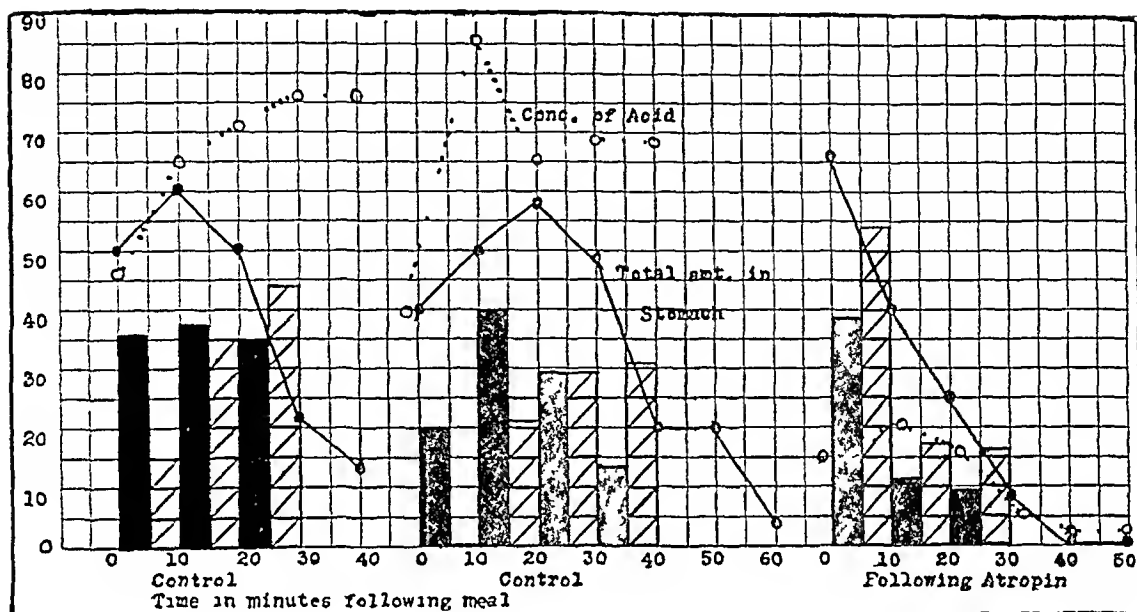


Chart 3—Observations in case 3

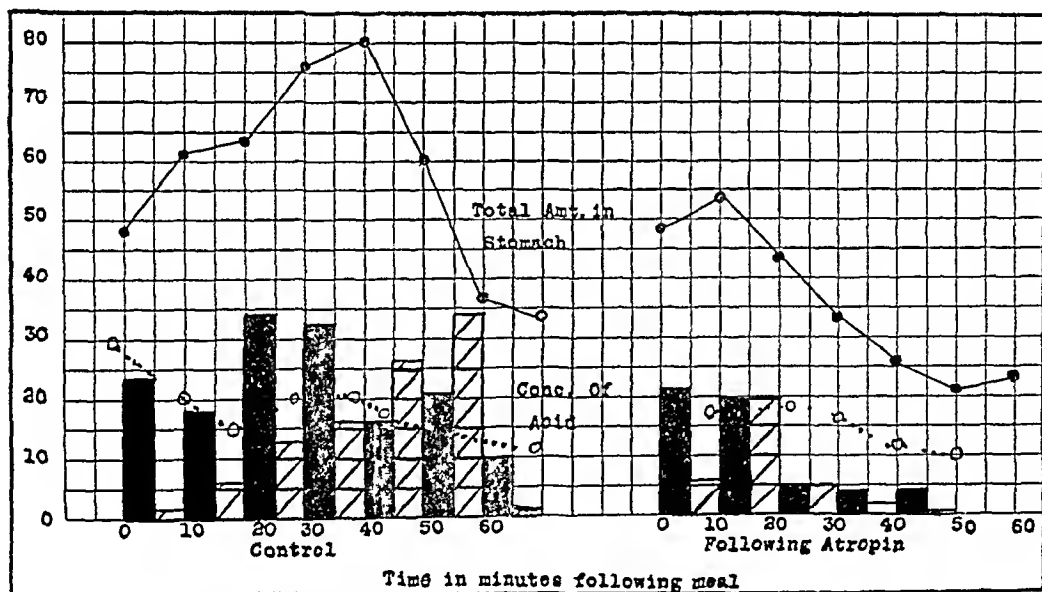


Chart 4—Observations in case 4

was, however, not sustained, and after the first ten minute period practically no juice was secreted. The stomach was empty at the same time after atropine as before, but the amount of juice passing the pylorus was very much less—26 cc in thirty minutes as against 75 cc. The curve of acidity was high and uniform before atropine, after the drug the curve was low and the abrupt fall indicates that as the secretion of juice diminished the acidity fell practically to zero.

TABLE 3—Case 3

Time of Observation	Total Stomach Contents, Cc	pH	Volume of Volume Dis- Juice Secreted charged in Titratable in 10 Minute 10 Minute Period Period			Remarks
			Titratable Acid Dimethyl phenolphthalein	Pure Juice	Pure Juice	
Without Atropine—November 12						
Immediately after test meal	50	1.0	10	14		
10 minutes after test meal	60	1.4	40	42	35.5	65
20 minutes after test meal	50	1.2	52	60	37.5	71
30 minutes after test meal	22	1.15	62	72	35.0	76
40 minutes after test meal	14	1.15	62	71		76
Without Atropine—December 1						
Immediately after test meal	40	2.1	1	6		
10 minutes after test meal	50	1.3	38	42	20	Pulse rate, 80
20 minutes after test meal	58	1.2	48	52	10	Pulse rate, 80
30 minutes after test meal	48	1.2	56	60	27	Pulse rate, 80
40 minutes after test meal	20	1.2	58	62	13	68
50 minutes after test meal	20	1.65	30		31	68
After Atropine, 1/30 Grain (2 mg.)—December 1						
Immediately after test meal	66		4	6		Pulse rate, 128, felt sleepy, arms weak
10 minutes after test meal	40	3.1	2	14	38	Pulse rate, 144
20 minutes after test meal	25	3.0	4	14	12	Pulse rate, 140
30 minutes after test meal	8	3.0	0	6	9.5	Pulse rate, 140, things looked smoky
40 minutes after test meal	1—	3.4	0			Throat very dry
50 minutes after test meal	1—	4.2	0			Pulse rate, 140

TABLE 4—Case 4

Time of Observation	Total Stomach Contents, Cc	pH	Volume of Volume Dis-			Remarks
			Titratable Acid Dimethyl phenolphthalein	Juice Secreted charged in Titratable In 10 Minute 10 Minute Period Period		
				Pure Juice	Pure Juice	
Without Atropine—December 8						
Immediately after test meal	48		2	6		
10 minutes after test meal	62		6	10	23.5	15
20 minutes after test meal	64	2.3	6	10	17.5	15
30 minutes after test meal	76	2.2	8	16	34.5	20
40 minutes after test meal	80	2.2	8	18	32.5	20
50 minutes after test meal	60	2.1	10	14	16.5	15
60 minutes after test meal	36	2.0	10	11	20.5	15
After Atropine, 1/30 grain (2 mg.)—December 8						
Immediately after test meal	48					
10 minutes after test meal	54	2.25	6	8	22	Pulse rate, 124
20 minutes after test meal	44	2.2	6	12	19	Pulse rate, 122
30 minutes after test meal	34	2.2	6	12	5	Pulse rate, 124
40 minutes after test meal	26	2.2	6	12	4	Pulse rate, 112
50 minutes after test meal	22	2.2	6	8	4	Pulse rate, 112
60 minutes after test meal	21	2.2	0		0	Pulse rate 112

CASE 7—D W, a man, aged 40, with hypertension (slight), had no gastric symptoms. The control test (table 7 and chart 7) showed a prompt secretion of rather large amounts of juice of high acidity. The volume of juice then steadily decreased and toward the end of the test there was a marked fall in acidity as

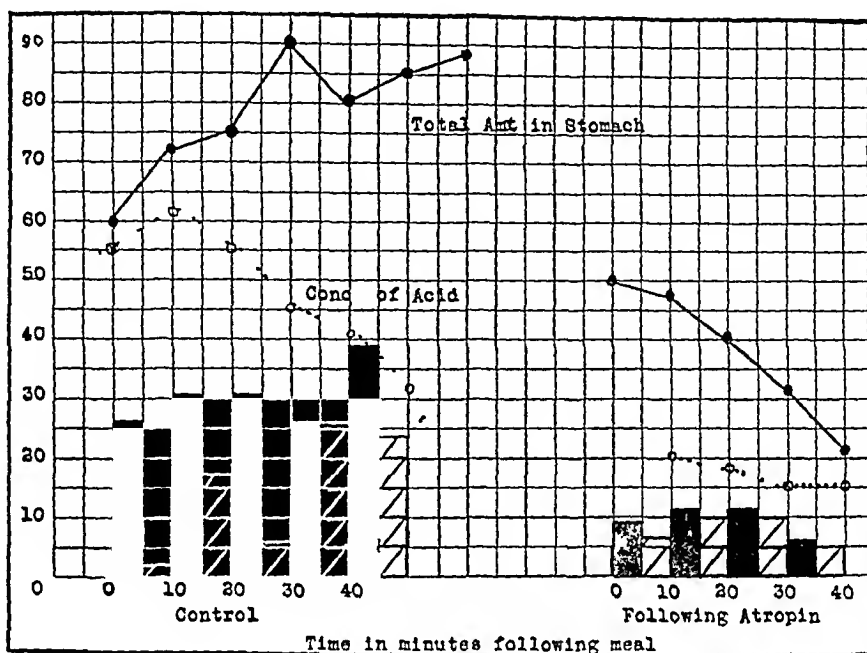


Chart 5—Observations in case 6

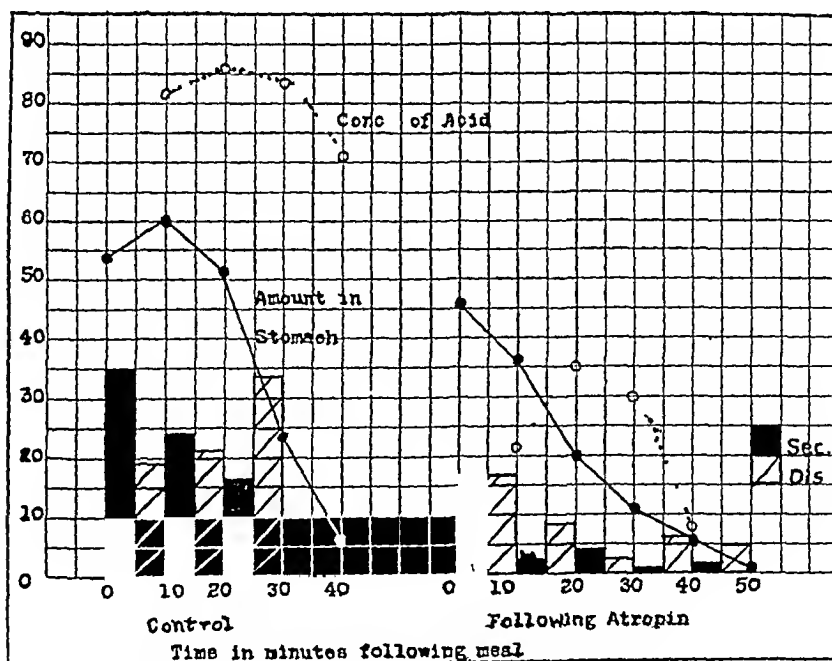


Chart 6—Observations in case 6

well. After atropine there was a brisk temporary response followed by secretion of only small quantities of juice. The same marked fall in acidity as before atropine was seen toward the end of the test. There was no striking alteration in motility.

TABLE 5—Case 5

Time of Observation	Total Stomach Contents, Gc	pH	Titratable Acid Dimethyl phenolphthalein	Volume of Juice Secreted changed in Titratable			Remarks
				Without Atropine—November 18	in 10 Minute Period	Acidity of Pure Juice	
Immediately after test meal	60	1.6	16	20	2.5	3.5	62
10 minutes after test meal	72	1.4	30	36	30.5	17.5	57
20 minutes after test meal	75	1.4	36	42	31.0	6.0	55
30 minutes after test meal	90	1.4	34	44	26.0	26.0	45
40 minutes after test meal	80	1.5	30	40	38.0	23.0	41
50 minutes after test meal	85	1.6	26	38			
After Atropine—November 18							
30 minutes after atropine	50	1.4	0	2	9	7	Pulse rate, 80
40 minutes after atropine	48	2.3	4	8	12	10	Pulse rate, 76
50 minutes after atropine	40	2.1	6	10	12	10	Pulse rate, 80
60 minutes after atropine	32	2.1	6	10	12	10	Pulse rate, 88
70 minutes after atropine	22	2.15	6	12	5.5	5	Pulse rate, 83

TABLE 6—Case 6

Time of Observation	Total Stomach Contents, Gc	pH	Titratable Acid Dimethyl phenolphthalein	Volume of Juice Secreted changed in Titratable			Remarks
				Without Atropine—November 10	in 10 Minute Period	Acidity of Pure Juice	
Immediately after test meal	54	1.9	14	16	35	19	Pulse rate, 82
10 minutes after test meal	60	1.2	38	16	24	22	
20 minutes after test meal	52	1.15	56	62	16	34	
30 minutes after test meal	24	1.1	62	70			
40 minutes after test meal	6	1.3	62	70			
After Atropine, 1/100 grain (2 mg.)—November 10							
25 minutes after atropine	46	3.3	0	0	16	16	Pulse rate, 90
35 minutes after atropine	36	2.4	4	8	2	8	Pulse rate, 128
45 minutes after atropine	20	1.9	8	14	2	35	
55 minutes after atropine	12	2.0	14	16	4	30	
65 minutes after atropine	6	2.0	2	1	1	7	
75 minutes after atropine	2	2.1			2	5	No other symptoms of atropine effect

CASE 8—G W, a man, aged 49, convalescent from bronchopneumonia, had a normal temperature for several weeks. He had never had any digestive symptoms. The two control examinations (chart 8 and table 8) showed essentially the same results—secretion of a moderate amount of juice of moderate acidity, with steady emptying of the stomach. After the administration of atropine the volume secreted

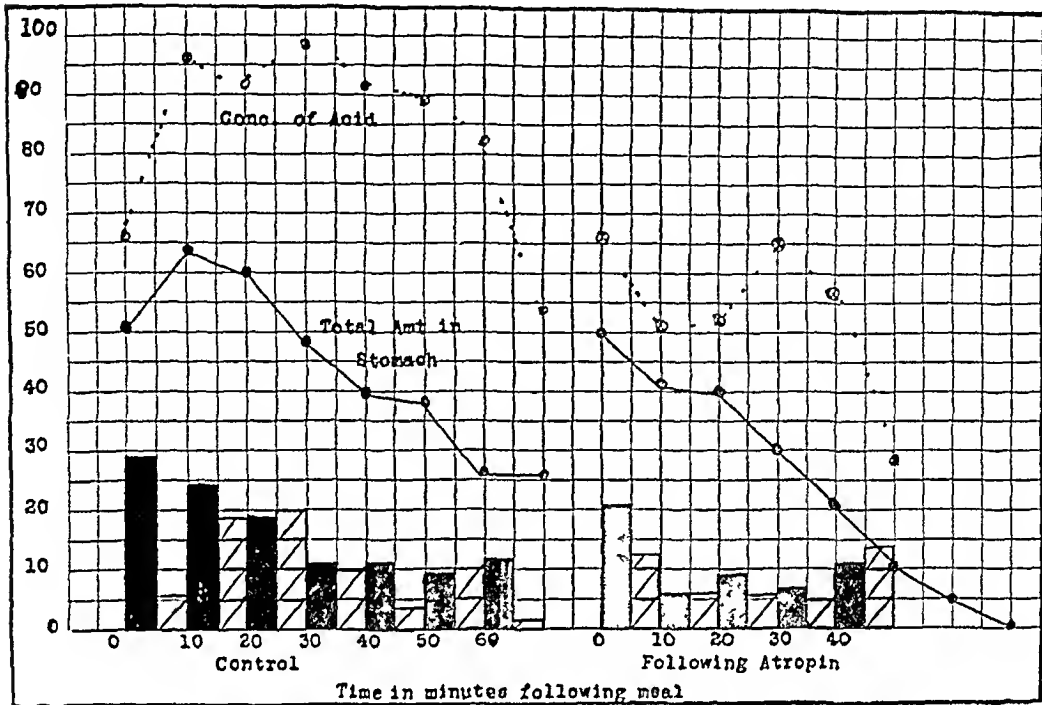


Chart 7—Observations in case 7

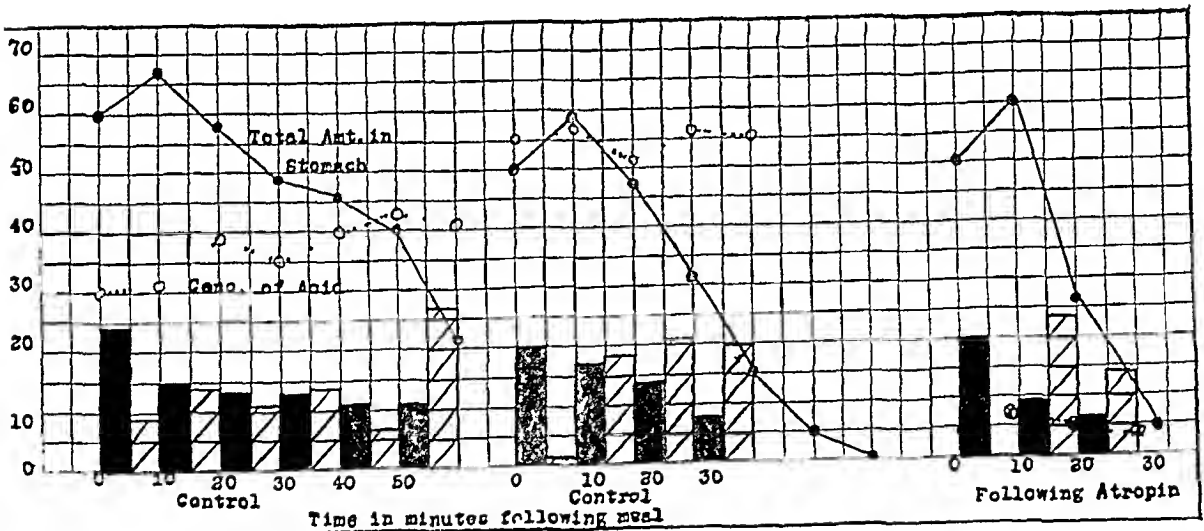


Chart 8—Observations in case 8

was somewhat diminished—34.5 cc in thirty minutes as against 52 cc and 53 cc, but the degree of acidity was tremendously reduced, free acid as measured with dimethyl being entirely abolished. The stomach was empty sooner after atropine than before, but the amount of juice discharged was much less—17 cc in thirty minutes as against 42 cc and 36 cc.

TABLE 7—Case 7

Time of Observation	Total Stomach Contents, Gc	pH	Titratable Acid Dimethyl phenolphthalein	Volume of Volume Dis			Remarks
				Juice Secreted charged in Titratable			
				in 10 Minute Period	10 Minute Period	Aldity of Pure Juice	
Without Atropine—December 8							
Immediately after test meal	52	1.8	8	10			
10 minutes after test meal	64	1.25	44	48	27.5	5.5	96
20 minutes after test meal	60	1.20	60	64	24.0	18.0	92
30 minutes after test meal	48	1.20	72	76	18.0	20.0	98
40 minutes after test meal	40	1.20	74	78	12.0	10.0	92
50 minutes after test meal	38	1.20	70	76	11.5	3.5	87
60 minutes after test meal	26	1.30	72	76	8.0	10.0	83
70 minutes after test meal	26	1.50	42	52	12.0	2.0	54
After Atropine, 1/100 gram (2 mg.)—December 11							
50 minutes after atropine	50	1.0	8	10			Pulse rate, 96
60 minutes after atropine	42	1.6	22	26	21.5	13.5	Pulse rate, 96
70 minutes after atropine	40	1.5	30	32	5.5	5.5	Pulse rate, 96
80 minutes after atropine	30	1.4	42	46	8.0	6.0	Pulse rate, 100
90 minutes after atropine	22	1.4	44	46	7.0	5.0	Pulse rate, 100
100 minutes after atropine	10	1.5	30	32	12.0	14.0	Pulse rate, 96
60 minutes after test meal	5	1.5					Pulse rate, 80
70 minutes after test meal	0						Pulse rate, 90

TABLE 8—Case 8

Time of Observation	Total Stomach Contents, Gc	pH	Titratable Acid Dimethyl phenolphthalein	Volume of Volume Dis Juice Secreted charged in Titratable in 10 Minute 10 Minute Period Pure Juice			Remarks
Without Atropine—October 21							
5 minutes after test meal	60	2.1	6	10			30
15 minutes after test meal	67	1.95	11	17	24.5	9.5	32
25 minutes after test meal	58	1.8	18	24	15.7	15	37
35 minutes after test meal	48	1.7	20	26	13	11	35
45 minutes after test meal	46	1.65	23	33	13	14	40
55 minutes after test meal	40	1.6	30	37	11.5	7	43
65 minutes after test meal	22	1.55	32	38	9	15	42
Without Atropine—November 10							
Immediately after test meal	50		12	14			Pulse rate, 84
10 minutes after test meal	58	1.45	18	22	20	2	Pulse rate, 88
20 minutes after test meal	47	1.45	24	34	17.5	18.5	Pulse rate, 80
30 minutes after test meal	32	1.4	30	40	14.5	21.5	Pulse rate, 84
40 minutes after test meal	15	1.4	34	46	7.5	20.0	Pulse rate, 80
50 minutes after test meal	5	1.4	40	50			Pulse rate, 80
After Atropine, 1/100 grain (15 mg.)—November 10							
Immediately after test meal	50	3.4	0	2			Pulse rate, 92, occasional systoles
10 minutes after test meal	60	3.5	0	2	20	0	Pulse rate, 84
20 minutes after test meal	26	3.4	0	2	9	23	Pulse rate, 86
30 minutes after test meal	5	3.4	0	2	5.5	14.5	Pulse rate, 81, no dryness of mouth, no dilatation of pupils

CASE 9—E G, a woman, aged 28, who had an old tuberculous peritonitis, was clinically well and had no digestive symptoms. The control examinations (table 9 and chart 9) showed secretion of small amounts of juice of rather high acidity. After atropine the secretion was practically abolished, although there was almost no change in the volume curve of the stomach contents. There was a marked clinical reaction to the atropine.

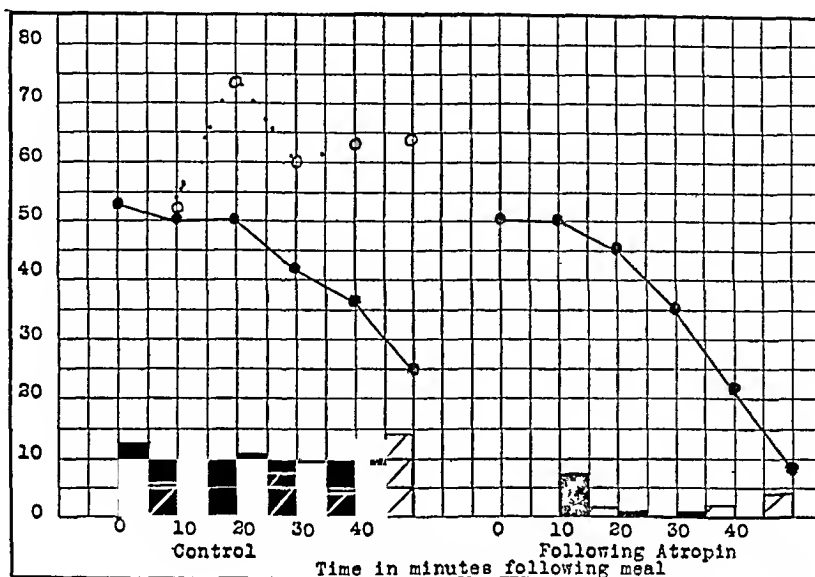


Chart 9—Observations in case 9

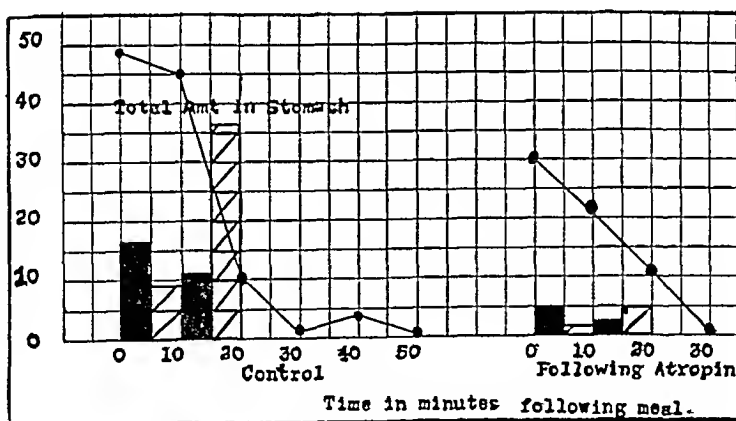


Chart 10—Observations in case 11

CASE 10—C G, a man, aged 24, was clinically diagnosed as normal. The control examination (table 10) showed very rapid emptying of the stomach. It was only possible to calculate secretion for one period of ten minutes during which 35 cc of juice was secreted. Two tests done after atropine showed marked differences in motility. In the second test it was seen that after a moderate initial response the secretion of juice was practically abolished. There was marked clinical atropine effect on both occasions.

CASE 11—S M, a man, aged 50, had pernicious anemia. Hemoglobin was 32 per cent. No digestive symptoms were present. The results of examination before and after atropine are shown in table 11. The volume of secretion, already

TABLE 9—Case 9

Time of Observation	Total Stomach Contents, Gc	pH	Without Atropine—December 7			Volume of Juice Secreted charged in Titratable Acidity of Pure Juice			Remarks
			Total Acid Dimethyl phenolphthalein	in 10 Minute Period	Volume Discharged in 10 Minute Period	in 10 Minute Period	Volume Discharged in 10 Minute Period	Aidity of Pure Juice	
Immediately after test meal	53	2.2	6	8					
10 minutes after test meal	50	1.8	16	18	12.5	5.5	50		
20 minutes after test meal	50	1.6	32	36	10.0	0.0	73		Pulse rate, 92
30 minutes after test meal	42	1.5	30	36	10.5	7.5	60		Pulse rate, 96
40 minutes after test meal	36	1.4	36	44	8.0	4.0	63		
50 minutes after test meal	25	1.5	40	46	13.0	14.0	64		
Immediately after test meal	50	3.2	0	4					
10 minutes after test meal	50	3.2	0	4	7.0	2.0			Pulse rate, 152, palpitation
20 minutes after test meal	15	3.2	0	4	0.5	0.0			Pulse rate, 156
30 minutes after test meal	35	3.4	0	4	0.5	0.0			Pulse rate, 144
40 minutes after test meal	23	3.6	0	4	0.5	1.5			Pulse rate, 156
50 minutes after test meal	9	4.0	0	6	0.0	4.0			Pulse rate, 144, slight nausea

TABLE 10—Case 10

Time of Observation	Total Stomach Contents, Gc	pH	Without Atropine—November 14			Volume of Juice Secreted charged in Titratable Acidity of Pure Juice			Remarks
			Total Acid Dimethyl phenolphthalein	in 10 Minute Period	Volume Discharged in 10 Minute Period	in 10 Minute Period	Volume Discharged in 10 Minute Period	Aidity of Pure Juice	
Immediately after test meal	40		6	10					
10 minutes after test meal	25	1.6	30	38	35	10	49		Pulse rate, 84
20 minutes after test meal	12		26	34					
Immediately after test meal	25		10	14					Pulse rate, 136
10 minutes after test meal	15	2.2	4	12	?	?			Pulse rate, 140
20 minutes after test meal	0				?	?			Pulse rate, 150, mouth dry, palpitation, cannot read
30 minutes after test meal	0.5	4.2							Pulse rate, 130
Immediately after test meal	50	5.2	0						Pulse rate, 132
10 minutes after test meal	43	2.4	2	6	14	21	13		Pulse rate, 132
20 minutes after test meal	32	2.4	2	6	18	15	18		Pulse rate, 132
30 minutes after test meal	20	2.3	4	8	1	4	10		Pulse rate, 136, nausea, headache, palpitation, cannot read
40 minutes after test meal	15	2.8	1	3	6	1	3		Pulse rate, 132
50 minutes after test meal	8	3.0	0	2	1	1	3		Pulse rate, 124

scant, was still further diminished and at the end of thirty minutes had apparently ceased. The drop in p_H from 7.2 to 6.6 does not indicate secretion of a more acid juice after atropine, the alkaline mucus of the stomach had been washed out and p_H 6.6 simply represents the p_H of the test meal.

CASE 12—A. M., a woman, aged 29, with stricture of the rectum and syphilis, had never had any gastric symptoms. This patient had no free hydrochloric acid (table 12) although the moderate amounts of juice which she secreted possessed some acidity as evidenced by the fall in the p_H of the stomach contents from 7.2 to 5.0. After atropine the secretion, already scant, was further reduced and eventually practically abolished, although it still contained some acid. There was no striking alteration in motility.

COMMENT

A survey of the foregoing protocols shows several striking facts:

1. The effect of atropine on the volume of gastric juice. In a general way it is immediately apparent that the amount of secretion is smaller after atropine than in persons not under the influence of the

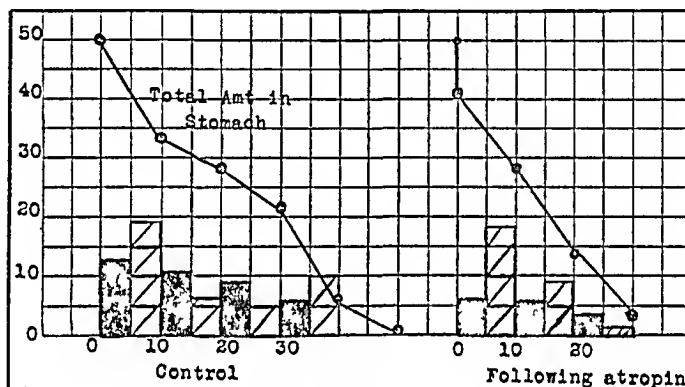


Chart 11—Observations in case 12

drug. There are several points about the type of reaction, however, which require special comment. In the control examinations secretion begins promptly after the introduction of the stimulus and usually is maintained at a steady level or gradually diminishes. After atropine on the other hand in many of the cases there was a prompt response that lasted only during the first ten minute period and was then followed by a marked diminution or even cessation of secretion. In other words, not only was the total amount of secretion diminished, but the type of secretion curve was markedly altered (cases 1, 3, 4, 6, 7, 8, 9 and 10). It is of interest also that the patients were well under the influence of atropine as evidenced by the clinical reaction at the moment when the test stimulus was introduced. Repeated aspiration showed that at this time the fasting secretion in most of the cases had ceased. In spite of this inhibition the test stimulus was still able to evoke secretion which in some cases (cases 3, 4, 7 and 8) was nearly as abundant during the

TABLE 11—Case 11

Time of Observation	Total Stomach Contents, Gc	pH	Titratable Acid Dimethyl phenolphthalein	Volume of Volume Dis- Juice Secreted charged in Titratable in 10 Minute 10 Minute Period Period		Remarks
				Without Atropine—December 1	Pure Juice	
Immediately after test meal	18		0			
10 minutes after test meal	15	7.2	0	16.0	8.0	Pulse rate, 88
20 minutes after test meal	10	7.2	0	10.5	35.5	
30 minutes after test meal	1	7.2	0			
				After Atropine, 1/100 grain (2 mg.)—December 1		
Immediately after test meal	33		0			
10 minutes after test meal	20	6.6	0	5	2	Pulse rate, 100
20 minutes after test meal	11	6.6	0	3	5	Pulse rate, 100
30 minutes after test meal	0		0			Pulse rate, 100

TABLE 12—Case 12

Time of Observation	Total Stomach Contents, Gc	pH	Titratable Acid Dimethyl phenolphthalein	Volume of Volume Dis- Juice Secreted charged in Titratable in 10 Minute 10 Minute Period Period		Remarks
				Without Atropine—December 2	Pure Juice	
Immediately after test meal	50	7.2	0	2		
10 minutes after test meal	34	7.0	0	4		
20 minutes after test meal	28	7.0	0	13	19	Pulse rate, 88
30 minutes after test meal	22	6.2	0	11	7	Pulse rate, 88
40 minutes after test meal	6	5.0	0	9	5	
				6	10	
				After Atropine, 1/100 grain (2 mg.)—December 7		
Immediately after test meal	42	7.0	0			Pulse rate, 128
10 minutes after test meal	27	7.0	0	5.5	18.5	Pulse rate, 136
20 minutes after test meal	14	5.0	0	5.5	8.5	Pulse rate, 128
30 minutes after test meal	1	5.2	0	3.5	1.5	Pulse rate, 120

first ten minute period as in the control examinations without atropine. These facts are shown quantitatively in table 13.

2 The effect of atropine on the degree of acidity of the gastric juice. Keeton, Koch and Luckhardt pointed out that in dogs the volume of juice diminished after atropine more rapidly than the acidity of the secretion. Under the conditions of our experiments this seems to be true in many instances but is not uniformly apparent. In case 3, for example, secretion was not diminished in the first ten minute period although the acidity was markedly decreased, and in case 9, in which there was no titratable free acid after atropine, a small but definite secretion of juice took place. On the other hand, as the secretion becomes markedly diminished it is clear that the acidity falls to low figures, although we have no data on the actual acidity of the juice as

TABLE 13—*Comparison of Volume of Secretion and Acidity Before and After Injection of Atropine*

Case	Volume Secreted in First 10 Minute Period		Total Volume Secreted		Highest Titratable Acidity	
	Before Atropine, Cc	After Atropine, Cc	Before Atropine, Cc	After Atropine, Cc	Before Atropine	After Atropine
1	70	21.5	192 (30 minutes)	36 (30 minutes)	74	37
2	59	12.0	168 (30 minutes)	46 (30 minutes)	95	90
3	35.5	38.0	108 (30 minutes)	59.5 (30 minutes)	76	20
4	23.5	22.0	124.5 (50 minutes)	54 (50 minutes)	20	19
5	25.5	9.0	113 (40 minutes)	38.5 (40 minutes)	62	20
6	35.0	16.0	75 (30 minutes)	22 (30 minutes)	86	35
7	27.5	21.5	93 (50 minutes)	54 (50 minutes)	48	65
8	24.5	20.0	53 (30 minutes)	34.5 (30 minutes)	43	8
9	12.5	?	54 (50 minutes)	8.0 (50 minutes)	73	0
10	35.0	14.0			49	18
11	16.0	5.0	265 (20 minutes)	8.0 (20 minutes)	0	0
12	13.0	5.5	33 (30 minutes)	14.5 (30 minutes)	0	0

secreted but only estimation of the titratable acidity of the stomach contents at various intervals after stimulation.

A summary of the actual quantitative relations is given in table 13.

3 Effect of atropine on motility of the stomach. A survey of the volume curves of stomach contents shows that the stomach almost invariably became empty sooner after atropine than before the drug was given. On the other hand, owing to lessened secretion less fluid passed the pylorus in a given time. Furthermore, there are normally (as will be pointed out in another article) great variations in the speed of emptying of the stomach as tested by this method and these variations are also seen after atropine. The results of repeated tests of motility in the same patients (not shown in the foregoing protocols) are summarized in table 14.

On the whole, then, there is no evidence in these tests that the motility of the stomach was essentially altered. The actual amounts of gastric contents discharged before and after atropine in relation to the emptying time are summarized in table 15.

SUMMARY

1 After doses of atropine large enough to produce outspoken clinical pharmacologic effects, the introduction of 50 cc of 7 per cent alcohol solution is followed by a secretion of gastric juice.

TABLE 14—*Emptying Time of Stomach on Successive Occasions After Injection of Atropine, One-Thirtieth Gram (Test Meal, 50 cc of 7 Per Cent Alcohol Solution)*

Case	Emptying Time (Minutes) First Test	Emptying Time (Minutes) Second Test	Emptying Time (Minutes) Third Test	Emptying Time (Minutes) Fourth Test
122	20	30		
126	5	20	20	30
138	5	20		
140	20	60		

TABLE 15—*Emptying Time of Stomach and Amount of Gastric Discharge Before and After Atropine*

Case	Before Atropine		After Atropine	
	Emptying Time, Minutes	Amount of Contents Discharged	Emptying Time, Minutes	Amount of Contents Discharged
1	50+ (70 cc still present)	92 (30 minutes)	60	37 (50 minutes)
2	50+ (64 cc still present)	136 (30 minutes)	60+ (75 cc still present)	29 (60 minutes)
3	60	80 (40 minutes)	40	87.5 (30 minutes)
4	70+ (34 cc still present)	96.5 (70 minutes)	60+ (24 cc still present)	32 (50 minutes)
5	60+ (88 cc still present)	76.0 (50 minutes)	40+ (22 cc still present)	32 (40 minutes)
6	40	75 (30 minutes)	40	38 (50 minutes)
7	70+ (25 cc still present)	69 (40 minutes)	60	70 (50 minutes)
8	50	62 (40 minutes)	30	37.5 (30 minutes)
9	50+ (25 cc still present)	31 (50 minutes)	50	7.5 (50 minutes)
10	40	11 (40 minutes)	30	28.5 (30 minutes)
12	30	43.5 (30 minutes)	30	7.0 (20 minutes)

2 This secretion takes place even after fasting secretion has been abolished.

3 The curve of secretion is altered as to form after atropine and the total volume of secretion is, as a rule, markedly diminished.

4 The degree of acidity is reduced, but there is no parallel relation between degree of reduction of volume and degree of reduction of acidity.

5 No definite changes in gastric motility can be ascribed to atropine in the present experiments.

THE TREATMENT OF POLYCYTHEMIA VERA (ERYTHREMIA) WITH PHENYLHYDRAZINE *

GEORGE E BROWN, M D

AND

HERBERT Z GIFFIN, M D

ROCHESTER, MINN

INTRODUCTION

The use of phenylhydrazine as a therapeutic agent followed its use experimentally in producing hepatic lesions, when destruction of the erythrocytes was noted Hoppe-Seyler ¹ in 1885 was the first to employ hydrazine experimentally in animals, and in 1908 Morawitz and Pratt ² used it specifically for the purpose of producing experimental anemia in animals Eppinger and Kloss ³ in 1918 were the first to apply it clinically in cases of polycythemia vera They observed a fall in the erythrocytes and hemoglobin, mild jaundice and dark urine Taschenberg ⁴ reported details of the treatment of a woman with polycythemia vera The patient had splenomegaly, the hemoglobin was 140 per cent, and the erythrocytes numbered 8,500,000 for each cubic millimeter She was given a total of 3 Gm of phenylhydrazine hydrochloride over a period of thirteen days, and a year later 4.25 Gm in twenty-one days, with definite effect on the blood and the development of jaundice each time Levi ⁵ reported a case of polycythemia vera in which 7.5 Gm of phenylhydrazine had been given daily over a period of one and one-half years The patient died from intercurrent disease Necropsy revealed "raspberry" bone marrow, splenomegaly, coronary sclerosis pneumonia and cirrhosis of the liver The possible effect of phenylhydrazine in the production of cirrhosis of the liver is of course of crucial importance Cirrhosis of the liver has been observed in cases of polycythemia in which no treatment was given, and may be related to overwork of the

* From the Division of Medicine, Mayo Clinic

* Read before the American Society for Clinical Investigation, Atlantic City, May 3, 1926

1 Hoppe-Seyler, G Ueber die Wirkung des Phenylhydrazins auf den Organismus, *Ztschr f physiol Chem* **9** 34-39, 1884-1885

2 Morawitz, P, and Pratt, J Einige Beobachtungen bei experimentellen Anamien, *Munchen med Wchnschr* **2** 1817-1819, 1908

3 Eppinger, H, and Kloss, K Zur Therapie der Polyzythamie, *Therap Monatsh* **32** 322-326, 1918

4 Taschenberg, E W Ueber die Behandlung der Polyzythamie mit Phenylhydrazin, *Deutsche med Wchnschr* **47** 774-775 (July 7) 1921

5 Levi, Ernst Ueber die Ursache der Lebercirrhose beim Polycythamie, *Ztschr f klin Med* **100** 777-784, 1924

liver from increase in the amount of blood destroyed Owen ⁶ reported five cases of polycythemia vera in which phenylhydrazine had been given over periods of months, with very definite destruction of blood, and the development of mild anemia He also noted the development of leukocytosis early in the administration of the drug, and suggested that the degree of leukocytosis might serve as an index of the amount of the drug required He believes that if leukocytosis is marked, it is safer not to give the drug until the leukocyte count is reduced The therapeutic results were quite satisfactory, and no harmful effects were observed

COMPOSITION OF PHENYLHYDRAZINE

The formula for phenylhydrazine is $C_6H_5NH NH_2$ Hoppe-Seyler has shown that in the experimental animal given phenylhydrazine subcutaneously the drug is very toxic, that it destroys red corpuscles by its reducing effect on hemoglobin, and is likewise a powerful protoplasmic poison Bodansky,⁷ while studying the injury to the liver caused by different hydrazine compounds, found marked destruction of the red corpuscles, hyperpigmentation of the spleen, and pigmentation with extensive degeneration of the liver in a dog weighing 5.9 Kg that had received subcutaneous injections of phenylhydrazine hydrochloride, totaling 360 mg In another experiment a decrease in the fructose tolerance was manifested after the first dose of 150 mg of the drug, and in twelve days the erythrocytes decreased from 5,640,000 to 910,000 for each cubic millimeter This change in the fructose test, before and after phenylhydrazine poisoning was interpreted as evidence of hepatic insufficiency Bodansky compares the effect of a number of derivatives of hydrazine acetyl phenylhydrazine, methyl phenylhydrazine, p-hydrazinbenzoic acid, diphenylhydrazine hydrochloride and others The formula of acetyl phenylhydrazine is $C_6H_5NH NHCOCH_3$ This was found to have a marked reducing effect on the hemoglobin but not of the same degree as phenylhydrazine In one experiment on a dog weighing 10.5 Kg two injections of acetyl phenylhydrazine, totaling 0.71 Gm, were given The animal became markedly anemic Very little destructive change could be demonstrated in the hepatic cells

Underhill and Karelitz ⁸ studied the carbohydrate metabolism in dogs injected with hydrazine sulphate, and found hypoglycemia and an

6 Owen, Trevor A Case of Polycythaemia Vera with Special Reference to the Familial Features and Treatment with Phenylhydrazine, *Bull Johns Hopkins Hosp* 35 258-262 (Aug) 1924

7 Bodansky, Meyer The Action of Hydrazine and Some of Its Derivatives in Producing Liver Injury as Measured by the Effect on Levulose Tolerance, *J Biol Chem* 58 799-811 (Jan) 1924

8 Underhill, F P, and Karelitz, Samuel, Jr The Influence of Hydrazine upon Blood Concentration and Blood Sugar Content, *J Biol Chem* 58 147-151 (Nov) 1923

increase in the concentration of the blood Wells⁹ investigated injury to the liver with the hydrazine compounds, and found a typical picture of fatty degeneration of the parenchymatous cells beginning at the center of the lobules and progressing outward As Owen¹⁰ has said, the importance of these observations lies in the fact that certain of the hydrazine compounds have a greater toxic effect on the liver than others The substitution of a methyl and acetyl group in the benzol ring, as shown by Bodansky, decreases the hepatic damage while the destructive effect on the blood is still retained At present we are using acetyl phenylhydrazine experimentally with a view to its later use in man

It will be noted that experimentally the hydrazine drugs are administered subcutaneously In one of our experiments 200 mg for each kilogram of body weight of the dog was given subcutaneously, marked destruction of blood occurred, and the animal died within five days When the drug is given by mouth, the toxic effects are much less In its clinical administration we have given the phenylhydrazine hydrochloride in capsules by mouth The low toxicity of the drug, when given by mouth to human beings, contrasts sharply with its effect on dogs when given subcutaneously

Experiments in vitro have been carried out on the effect of phenylhydrazine on erythrocytes No hemolytic effect occurred with varying dilutions of the drug in test tubes Data on the mode of excretion of the drug are lacking

METHODS OF STUDY¹¹

The total circulating plasma and blood volumes were ascertained by the dye method,¹² congo red being employed Circulating hemoglobin was estimated by multiplying the grams of hemoglobin per cent by the total circulating blood volume The acid hematin method was used for determining the hemoglobin, the normal standard of 15.6 Gm for each 100 cc of blood was used as 100 per cent Bromsulphalein was used to study hepatic function The fructose tolerance test was carried out in three cases Quantitative determinations of the size and number of capillaries of the skin were made during different periods of the disease

9 Wells, H. G. The Pathological Anatomy of Hydrazine Poisoning, *J Exper Med* **10** 457-464, 1908

10 Owen, Trevor. The Treatment of Erythemia with Phenylhydrazine, *J A M A* **85** 2027-2032 (Dec 26) 1925

11 Brown, G. E., and Giffin, H. Z. Studies of the Capillaries and Blood Volume in Polycythemia Vera, *Am J M Sc* **166** 489-502 (Oct) 1923, Studies of the Vascular Changes in Cases of Polycythemia Vera, *Am J M Sc* **71** 157-168 (Feb) 1926

12 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16** 547-576 (Oct) 1915, also *Tr A Am Phys* **30** 102-106, 1915

STUDIES DURING TREATMENT

The effect of phenylhydrazine hydrochloride in destroying blood is decisive. Its exact mode of action is not known, however, it is known to exert a reducing action on hemoglobin. Hemoglobin is split into its pigment and protein fractions. The destruction of the cells occurs early, an increase of serum bilirubin having been noted after the second dose of the drug, that is, after 0.2 Gm. has been given. The urine becomes progressively darker, keeping pace with the destruction of the blood. In all our cases sufficient amounts of the phenylhydrazine have been given to produce definite anemia. The effect of the drug was discernible for from seven to ten days after it had been discontinued, a further decrease of approximately 1,000,000 cells occurring. We have borne this fact in mind in regulating the dose, lately discontinuing the drug when the erythrocytes became decreased to approximately 4,500,000 for each cubic millimeter. The leukocytes showed the characteristic increase described by others, in one case (case 3) reaching 53,000. The leukocytosis persisted for varying periods, in one case for at least two months. The effect on the blood platelets was followed in three cases. In two the count was normal, in one the platelet count was high at the beginning of treatment and gradually diminished until it was about normal when the patient was dismissed from observation. The change in blood volume was striking. As the drug acts selectively on the erythrocytes, the change in the total blood volume is due largely to a decrease in the circulating cell volume. When a moderate degree of anemia is approached, the plasma volume increases, as has been described by Keith in cases of secondary anemia due to loss of blood. This change, however, is not marked and appears only when there is definite evidence of anemia. There was also a loss in the total amount of circulating hemoglobin of from 1.1 to 3.3 Kg. The serum bilirubin curve rose with a direct relationship to blood destruction. Jaundice usually appeared after 2.5 Gm. of phenylhydrazine hydrochloride had been administered, at this time the serum bilirubin was usually more than 4 mg. for each 100 cc. of blood. The sclerae were definitely stained and the skin in two cases was perceptibly jaundiced.

Study of hepatic function, both before and after the administration of phenylhydrazine hydrochloride, has shown no retention of bromsulphalein¹³. Determinations were made during different stages of destruction of blood. The fructose tolerance test made in three cases was satisfactory. The renal function showed no significant changes. Studies on the protein metabolism of the blood and urine during the period of

13 Greene, C. H., and Conner, H. M. Diseases of the Liver, V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, Arch. Int. Med., to be published.

destruction of blood have been carried out in detail. It has been shown that there is a marked increase in the output of urinary nitrogen during the period of blood destruction, accompanying increases were demonstrated in the blood urea. These findings will be discussed in detail by Huffman¹⁴. Electrocardiographic studies of the heart before and after administration of the drug showed no significant changes.

SYMPTOMS DURING TREATMENT

There were no marked symptoms that could be ascribed to the local effects of phenylhydrazine hydrochloride. Gastric symptoms were not observed during the first three or four days of treatment. The various symptoms observed later were associated with jaundice and the rapid destruction of blood, and presented clinical features that would be expected during a hemolytic crisis, varying from very mild to very severe reactions. The symptoms associated with jaundice were mild. Definite pruritis was not present, although a little itching occurred in two cases. In one case there was a slight irritation of the bladder. In three cases there were gastric disturbances, nausea and vomiting, these were the cases in which there was marked destruction of blood. Anorexia was constant. Weakness, insufficient to prevent patients from being up and about, was invariably noted during the period of rapid destruction of blood.

One patient (case 4) developed jaundice, slight enlargement of the spleen and liver, abdominal distress and nausea. Then, rather suddenly, all these symptoms became very much worse and were associated with pain in the region of the spleen. Hematuria and slight hematemesis occurred. Undoubtedly a severe type of hemolytic crisis was present in this case, and in addition to this there may have occurred an infarction of the spleen and, possibly, also of the kidney. All these symptoms cleared up within a few days. In another case thrombosis of the basilic vein of the arm developed the day after treatment had been discontinued, following an intravenous injection to estimate hepatic function. In a third case a similar condition developed in a superficial vein of the left leg independent of any sort of injection or treatment (case 7). This thrombotic vein was resected and a microscopic examination showed a subacute thrombosis with erythrocytes, fibrin and a few fibroblasts. A month later the vein was palpable as a firm, hard cord. It is impossible to be certain that these instances of thrombosis are directly related to the phenylhydrazine treatment, as thrombosis is common in cases of untreated polycythemia vera, even when the blood volume is not extremely high. On the other hand, it is possible that thrombosis may have a direct relation to the rapid destruction of blood and the liberation of thromboplastic material during treatment.

14 Huffman, L. D. Personal communication to the authors.

LATE EFFECTS OF TREATMENT

Patients have been traced after their dismissal from the clinic. The results have been satisfactory in all but one patient (case 2), who had marked hypertension. This did not decrease appreciably during treatment, and suboccipital headaches, mental irritability and weakness persisted. There was no evidence of deleterious effects from the use of phenylhydrazine in any of the cases. The maximal beneficial effects of treatment were evident in from three to six weeks after destruction of blood had ceased. Vertigo, fulness in the head, neuralgia, weakness and mental irritability disappeared in all but the one case noted. There were no significant changes in body weight. Intolerance to heat disappeared. The most striking improvement was the relief from pain. Two patients (cases 5 and 7) had had pain in the legs during exercise and clinical evidence of partial vascular obstruction (endarteritis obliterans). Complete relief was obtained while they were under observation, one month and one year, respectively. In case 6 there was lumbago of long standing with arthritic pains in the knees, the roentgen-ray examination showed a mild hypertrophic arthritis. Marked relief from pain followed the use of phenylhydrazine, but there was a gradual return of symptoms when the erythrocytes increased to approximately 6,000,000, with a return of the erythrosis and especially fulness of the head and vertigo. The length of time before the reappearance of symptoms has varied from three to six months. We have advised our patients to desist from further treatment until the symptoms became sufficiently troublesome to warrant it. The symptoms seem to be more important than the blood count in determining when further treatment is necessary.

DOSE OF THE DRUG

There is a considerable difference in patients with respect to their reaction to phenylhydrazine hydrochloride. The total amount of the drug given in order to obtain approximately the same effect in different patients varied from 3.4 to 7.6 Gm. Even when the dose is calculated on the basis of body weight and the amount of circulating hemoglobin destroyed, there is a marked difference in the amount of drug necessary. The average amount of hemoglobin destroyed by each gram of phenylhydrazine hydrochloride for each kilogram of body weight was 6 Gm (table 15).

Examinations of the blood have not been made often enough, nor over long enough periods to draw positive conclusions concerning tolerance to the drug and the effect of repeated treatment with the drug. The original or initial dose has been repeated in each case. In case 1 a second course of the drug, totaling 9 Gm, was taken four months after the first course, without any noticeable result, the preparation was

probably inert Two grams of a different brand of the drug gave symptomatic relief Seven months later the erythrocytes numbered 6,000,000 In case 7 the initial total dose was repeated six months later, with complete relief from symptoms, but the patient did not become noticeably pale as he had after his first treatment This man returned again a year after his first treatment and the original dose of 4.5 Gm was as effective as formerly

REPORT OF CASES

CASE 1—*History*—A man, aged 62, came to the clinic complaining chiefly of attacks of vertigo, which appeared suddenly and lasted a few seconds They had persisted for two and one-half years, and had become increasingly frequent during the last year He had also complained of numbness in the arms and shoulders, aching in various parts of the body, and general weakness His appetite had become excessive and he suffered from constipation Polyuria had been present for four years He said that one maternal uncle had had a very red complexion

Examination—The patient was thin, weighing 132 pounds (59.9 Kg) He was restless, consequently making purposeless motions, mentally irritable and somewhat melancholic The mucous membranes were cyanotic and the skin of the face, hands and feet was reddish blue Cold produced marked cyanosis, and the skin was dry and scaly Cardiac dulness measured 10 cm to the left, and the heart sounds were somewhat indistinct, an occasional extrasystole was present The edges of the spleen and liver were both palpable The peripheral blood vessels were not definitely sclerotic and the arteries of the feet seemed to be open The retinal veins were markedly distended The systolic blood pressure was 130, and the diastolic 85 The urine contained a trace of albumin and a few hyaline casts The hemoglobin was 148 per cent by the acid hematin method (22.5 Gm for each 100 cc), the erythrocytes numbered 7,850,000, and the leukocytes 6,200 The relative viscosity of the blood was 13.2 The blood urea was 16 mg, creatinine 1.6 mg, and uric acid 2.9 mg for each 100 cc The total blood volume was 11,000 cc, or 180 cc for each kilogram of body weight, whereas the cell volume by hematocrit was 67 per cent The basal metabolic rate was +37 A test of hepatic function by the dye method showed no retention, and the serum bilirubin was 0.7 The duodenal contents showed 1,000 units of urobilin and no urobilinogen A fragility test of the red cells was normal The clinical diagnosis was polycythemia vera

Treatment—The patient was given a total dose of 7.7 Gm of phenylhydrazine hydrochloride over a period of thirty-five days The total blood volume became reduced from 11,000 to 5,800 cc (103 cc for each kilogram of body weight), the hemoglobin from 22.5 to 11.5 Gm for each 100 cc, and the erythrocytes from 7,850,000 to 2,640,000 Four grams of the drug was given first with only very slight effect An additional 3.7 Gm was administered, during which time the destruction of blood became marked Repeated tests of hepatic function by the dye method showed no retention following treatment, while the phenol-sulphonphthalein estimation at the termination of treatment was 55 per cent The basal metabolic rate had fallen from +37 to -4 Symptomatically the improvement was striking the patient was quite free from his former symptoms, vertigo, mental irritability and restlessness having entirely disappeared He was definitely pale with a trace of icterus

This was the first case under our observation treated by phenylhydrazine The result was very satisfactory despite the development of rather marked anemia We were unable to demonstrate any effect on the function either of the liver or the kidney The patient's symptoms recurred in six months and a similar course of treatment was given

TABLE 1—*The Blood (Case 1)*

Date.	Hemoglobin		Leuko- cytes	Reticu- late Vis- cosity (Hess)	Cells by Hemato- crit, Cent	Blood		Plasma		Total Cir- culating Hemo- globin, Gm	Serum Bili- rubin, Mg	Total Dose of Drug, Gm	Clinical Notes
	Grams, per Cent	Pct Cent	1 rylthro- cytes, Millions			Volume, Cc	Cc for Each Kg of Body Weight	Volume, Cc	Cc for Each Kg of Body Weight				
1921													
12/15	22.5	118	7.85	13	67	11,000	183	3,640	60	2,470	1.7	1.0	Body weight, 60 kg
12/28	21.4	110	7.20		63	7,970	112	2,950	52	1,700			
1925													
1/11	19.9	140	5.70		65	9,900	173	3,460	60	1,970		3.4	Pallor 1
2/4	16.0	105	5.27	8	56	8,520	157	3,750	69	1,360	2.15	4.1	Slight jaundice
2/11	12.4	81	4.62		40	6,500	116	3,900	70	800		7.6	Patient dismissed, sympto- matically much improved
2/16	11.5	75	2.64		39	5,800	103	3,530	63	660	1.26		Second course of drug (9 Gm) with very little effect, inferior drug used
4/4	18.0	118	3.32									2.0*	Patient well, no recurrence of symptoms
11/14	18.2	119	6.53										

* Taken during July

at home with satisfactory result Ten months after the first period of treatment another course was given, however, no increase in the dosage was necessary in the subsequent treatments to produce a satisfactory relief from symptoms (tables 1 and 2) The patient stated in a recent letter that 0.3 Gm a week would keep him symptomless

CASE 2—History—A man, aged 56, came to the clinic because he had had headaches and stomach trouble for the last two years Pains in the right shoulder and arm had been diagnosed neuritis He was also told that he had high blood pressure Later severe attacks of pain accompanied by nausea and vomiting had occurred in the occiput every three or four days, these persisted up to the time of examination He had complained of ringing in the ears, severe vertigo, blurring of vision, and dyspnea on moderate exercise Constipation and slight loss of appetite had been constant during the last year There was no definite family history of polycythemia

Examination—The patient was well nourished, weighing 150 pounds (68 Kg) The systolic blood pressure was 192, and the diastolic 140 The face, hands and feet were reddish purple and cold, but arterial pulsation was normal The mucous membranes of the mouth and tongue were markedly cyanotic The spleen was

TABLE 2—Renal and Hepatic Function (Case 1)

Date,	Renal Function			Hepatic Function		Urine							Total Dose of Drug, Gm
	Phenol sulphophthalcin, per Cent	Blood Urea, Mg	Blood Creatinine, Mg	Dye Retention, Grade 0 to 4	Serum Bilirubin, Mg	Grade 0 to 4							
						Color	Bile	Albumin	Erythrocytes		Leukocytes	Urobilin	
									Casts				
12/18 1924	40	16	1.6	0	0.7			1	1	0	1	0	
2/ 4 1925	55	45	1.8	0	2.45	Black	+	1	0	1	1	0	4.4
2/12		48	2.2		1.26	Dark brown	+	1	0	0	1	0	7.7

just palpable, the liver was not felt The peripheral vessels were markedly tortuous and somewhat thickened The retinal arteries were constricted and the veins enlarged There were edema of the disks and small retinal hemorrhages and exudates The urine contained a moderate trace of albumin and a few erythrocytes The specific gravity varied from 1.010 to 1.026 The phenolsulphophthalein secretion was 55 per cent in two hours The hemoglobin was 29.4 Gm for each 100 cc of blood, the erythrocytes numbered 8,530,000, and the leukocytes 6,400 The fragility of the erythrocytes was normal The platelets were diminished in number, the coagulation time by the Boggs method was three minutes, the bleeding time one minute, and the relative viscosity 12 A study of the chemistry of the blood showed 45 mg of urea, 1.8 mg of creatinine, and 2.9 mg of uric acid for each 100 cc of blood The blood sugar was 0.089 mg for each 100 cc of blood Tests of hepatic function showed no retention by the dye method, the serum bilirubin was 0.9, and the fructose tolerance test was normal The total blood volume was 12,400 cc (190 cc for each kilogram of body weight) By hematocrit there was 72 per cent erythrocytes The vessels of the leg were normal from roentgenologic examination A diagnosis was made of polycythemia vera, severe essential hypertension with arteriosclerosis, and cardiac hypertrophy with slight insufficiency

Treatment—The patient was given a total dose of 6.4 Gm of phenylhydrazine over a period of sixteen days During the treatment, destruction of blood was marked, the total volume being reduced to 5,050 cc (81 cc for each kilogram of

TABLE 3—*The Blood (Case 2)*

Date, 1925	Hemoglobin		Leuko- cytes	Rela- tive Vis- cosity (Hess)	Cells by Hemato- crit, Cent	Blood		Plasma		Total Cir- culating Volume of Hemo- globin, Gm	Serum Bili- rubin, Mg	Total Dose of Drug, Gm	Clinical Notes
	Grams, per Cent	Per Cent				Volume, Cc	Cc for Each Kg of Body Weight	Volume, Cc	Cc for Each Kg of Body Weight				
1/12	20.1	103	853	15	72	12,400	190	3,460	51	3,640	0.9		Body weight, 68 Kg, blood pressure, 190/140
1/28 5/6	23.4 20.8	153 136	612 497	12 9.6	70 60	11,100 8,750	173 136	3,300 3,500	52 55	2,500 1,820	2.4	2.6 5.3	May 2, headaches disap- peared, May 10, sclera, jaundice 1
5/15 5/19	12.5 9.5	82 62	331 220	4	37	5,050	81	3,180	51	630	4.3	6.4	Phlebitis of left basile vein, blood pressure, 196/ 120, weight, 69 Kg
5/26 6/17*		75	340										Patient dismissed Color normal, occasional mild vertigo

* Following dismissal tests of the blood were carried out by Dr. Thor Jäger, Wichita, Kan.

body weight), and the cell volume was 37 per cent by hematocrit. The erythrocytes numbered 4,520,000 when the drug was stopped. However, the number of erythrocytes became further reduced to 2,180,000, and the hemoglobin to 9.5 Gm within a period of ten days after treatment was discontinued. Then evidence of destruction of blood ceased, during this period the blood urea increased to 72 mg for each 100 cc of blood, the creatinine to 3.8 mg, and the serum bilirubin to 4.3 mg. At this time the patient was definitely jaundiced and had bile in the urine. The phenolsulphonphthalein secretion at the time of the patient's dismissal was 35 per cent in two hours, and the test of hepatic function by the dye method showed no retention. The fructose tolerance test was unchanged. Thrombosis of the left basilic vein developed on the tenth day of treatment, following the injection of bromsulphalein, but subsided in three weeks. The systolic blood pressure following the initial period of rest was reduced to 180, and the diastolic to 120. After completion of treatment the systolic blood pressure was 196 and the diastolic 120, this level was maintained during the subsequent period of observation. Clinical and symptomatic improvement was very definite following treatment. The severe headaches and dizziness disappeared. The patient was allowed to return home and subsequent reports were kindly furnished by his physician. One month after his dismissal the erythrocytes numbered 2,800,000, and the leukocytes 12,000, hemoglobin by the Sahli method was 65 per cent. The phenolsul-

TABLE 4—*Renal and Hepatic Function (Case 2)*

Date, 1925	Renal Function		Hepatic Function		Urine							
	Phenol- sulphon- phthalein, per Cent	Blood Urea, Mg	Blood Creat- inine, Mg	Dye Re- tention Grade 0 to 4	Serum Bil- rubin, Mg	Color	Bile	Grade 0 to 4				
								Uro- bilin	Albu- min	Casts	Eryth- ro- cytes	Leuko- cytes
4/18	55	45	1.9	0	0.9		0	0	1	0	1	
4/28	60	38	1.6				0		1	Granular 1	1	
5/ 1				0	2.4	Dark brown						
5/ 6	35	52	2.2			Black	+		1	0	1	
5/15		72	3.8		4.3	Less dark	+		1	0	1	

phosphthalein excretion was 60 per cent for two hours, and the blood urea was 35 mg for each 100 cc of blood. Two weeks later the erythrocytes had increased to 3,400,000 and the leukocytes numbered 8,000, the hemoglobin was 75 per cent. Two months later the patient wrote that he felt his symptoms recurring, and he was advised to repeat the treatment. Symptoms recurred again six months after the second treatment.

The interesting points in the review of this case are (1) the lack of response of the blood pressure to a marked reduction in the circulating volume and viscosity of the blood, (2) relief for six months from symptoms that would ordinarily be ascribed to the hypertension, and (3) the absence of any demonstrable renal injury following treatment by phenylhydrazine when the presence of definite arteriosclerosis with probable pathologic changes in the kidneys would permit of marked susceptibility of this organ to toxic agents. There was no demonstrable hepatic damage, according to the tests of hepatic function. The development of marked anemia following the discontinuance of phenylhydrazine is also to be noted (tables 3 and 4).

CASE 3—History—A man, aged 43, came to the clinic because of vomiting, general weakness, fatigue, lumbago and occasional headaches, symptoms that began three years before, following dengue fever. He had been intolerant to heat and had become very nervous and excitable. During the preceding year he had vomited every morning. Eighteen months previously the extraction of teeth had been followed by a brisk hemorrhage which left him weak but symptomatically much improved. He had lost 20 pounds (9 Kg). For six months his symptoms had been getting worse until at the time of admission he could walk but short distances. His wife had noticed an increasing purplish color of the skin. There was no record in the family history of a similar condition.

Examination—The patient was well developed and weighed 147 pounds (66.7 Kg). The face and hands were very red and the conjunctiva injected. The mucous membranes of the mouth were reddish blue. The heart measured 11 cm to the left. The systolic blood pressure was 160, and the diastolic 120. The spleen was enlarged to the navel, 13 cm below the costal margin, and was not tender. The liver was not palpable. There were external hemorrhoids. The urine was normal. The acid hematin hemoglobin was 180 per cent, the erythrocytes numbered 7,480,000, and the leukocytes 6,700. The whole blood volume was 13,530 cc (202 cc for each kilogram of body weight), and the erythrocytes by hematocrit were 69 per cent. The number of platelets was normal. The coagulation time was six minutes by the Boggs method, the bleeding time one and one-half minutes, and the relative viscosity of the blood much increased, 11.8. The phenolsulphonphthalein excretion was 65 per cent in two hours. The fragility of the erythrocytes was normal. The retinal veins were markedly engorged and cyanotic, and the retinal arteries mildly sclerotic. The diagnosis was polycythemia vera.

Treatment—The patient received a total dosage of 6.1 Gm of phenylhydrazine hydrochloride during a period of sixteen days. There was a sharp decrease in the circulating blood volume and at the end of treatment very definite anemia. The platelet count throughout the entire period of observation was normal or slightly below normal, and marked leukocytosis developed. There was a decrease in the circulating blood volume of 5,000 cc, or approximately 50 per cent. An extreme reduction in hemoglobin and red cells occurred. Marked jaundice developed. The spleen increased in size during the height of destruction of blood, and the liver became palpable. During the peak of destruction the patient complained of pain in the epigastrium, extreme weakness and slight nausea. The urine became dark red, but no erythrocytes were found on microscopic examination. The blood urea increased and the phenolsulphonphthalein excretion decreased to 25 per cent. After the drug had been discontinued, destruction of blood continued for six days, but the patient's general condition rapidly improved and he felt quite normal, except for moderate weakness at the time of dismissal. The spleen had become reduced to one-half its former size. The liver was 5 cm below the costal margin. Subsequent blood counts were obtained through the courtesy of his home physician. A recurrence of symptoms took place three months after his dismissal, at which time erythrocytes numbered 8,000,000 for each cubic millimeter. A course of phenylhydrazine of the same dosage as the initial treatment gave complete relief from symptoms (tables 5 and 6).

The patient at the time of admission showed marked nervous irritability, restlessness and extreme weakness. The spleen was unusually large, extending to the navel. In spite of the extreme manifestations of the disease a prompt reduction in the blood volume and amelioration of the symptoms occurred. A severe anemia developed, without, however, symptoms that would ordinarily be associated with anemia, and from which the patient rapidly recovered. The renal function, according to the dye test, decreased from 65 to 25 per cent. The spleen

TABLE 5—*The Blood* (Case 3)

Date, 1925	Hemoglobin			Leuko- cytes	Rela- tive vis- cosity (Hess)	Cells by Hemato- crit, per Cent	Blood		Plasma		Total Cir- culating Volume of Hemo- globin, Gm	Serum Bili- rubin, Mg	Total Dose of Drug, Gm	Clinical Notes
	Grams, per Cent	Per Cent	Per Cent	Millions	Volume, Cc	Volume, Cc	Volume, Cc	Weight of Body Weight	Volume, Cc	Weight of Body Weight				
7/24	27.1	180		7.4	16	69	13,530	202	41,000	62	3,700	1.7		Fructose tolerance test negative, body weight, 67 Kg
8/5	21.4	160		7.1	11.8	68	10,600	160	31,000	51	2,580		1.6	Jundice 1, red fading
8/7				6.22										
8/10	24.0	157		6.28	9.2	51	8,600	138	35,000	55	2,080	6.9	3.2	
8/17	14.0	92		1.25	5.6	37	5,950	93	3,700	58	830	3.5		
8/21	8.6	56		2.65								3.67		Pain in epigastrium, weak- ness, insomnia
8/26	6.6	43		2.03	2.1	15	5,500	87	1,670	72	390	1.87	6.0	Spleen larger, not tender, jaundice 2
8/31	4.5	29		2.0	3.0									
11/5*		115		8.8										Feeling much better ex- cept for some weakness Spleen reduced, red color returning weakness weight, 67 Kg

* Blood count made by Dr. Robert Harris of Miami, Fla.

became reduced to half its former size. A second course of treatment with the same dosage became necessary three months later, and was followed by satisfactory results.

CASE 4—History—A woman, aged 31, came to the clinic complaining of indigestion and recurring attacks of migraine, consisting of severe frontal headaches, vertigo, and specks of fire before the eyes, which were relieved by vomiting but had continued for the last six years. She slept poorly, was easily fatigued, and was constipated. An abdominal exploration and cholecystectomy had been performed two years previously elsewhere. A tumor was then noted in the left upper quadrant. The family history contained nothing of significance.

Examination—The patient was thin and asthenic with skin moderately pigmented and dusky, reddish blue, especially on the face, neck, hands and arms. The finger nails were cyanotic and the pharynx and mucous membranes of the mouth were a deep reddish blue. The size of the heart and the heart sounds were normal. The systolic blood pressure was 120, and the diastolic 90. The spleen extended 4 cm. below the costal margin. The liver was not palpable. The peripheral arteries were soft and the veins distended. The nail capillaries were distended and the number of open capillaries for each square millimeter of skin on the back of the hands was about double the normal number. The fundi were essentially normal except that the retinal veins were a little darker and fuller

TABLE 6—Renal and Hepatic Function (Case 3)

Date, 1925	Renal Function			Hepatic Function		Urine				
	Phenol sulphon phthalein, per Cent	Blood Urea, Mg	Blood Creat- inine, Mg	Dye Re- tention, Grade 0 to 4	Serum Bili- rubin, Mg	Color	Grade 0 to 4			
							Albu- min	Casts	Eryth- rocytes	Leuko- cytes
7/24	65	27	15	0	17		1	Hyalin, 1	0	1
8/7		39		0	68		1			1
8/13	25	42		0	49		1		1	1
8/17	25	174	34		53	Dark brown	1		1	1
8/19		203	32			Dark brown	Trace			1
8/22	25	52		0	36	Dark brown	2			1
8/26		52	15	0	187	Dark brown				
8/28		36				Clear ring				
8/31		25								

than usual. The range of the specific gravity of the urine was normal. The sediment contained a few erythrocytes and 50 leukocytes to the low power field. The phenolsulphonphthalein excretion was 50 per cent in two hours. The erythrocytes numbered 6,890,000, and the leukocytes 9,500, the hemoglobin was 19.4 Gm. for each 100 cc. of blood, and 127 per cent by the acid hematin method. The whole blood volume was 7,700 cc. (167 cc. for each kilogram of body weight), and the erythrocytes by hematocrit were 71 per cent. The platelet count was normal. The coagulation time by the Boggs method was eight minutes, and the bleeding time one minute (table 7). The diagnosis was polycythemia vera and migraine.

Treatment—During the height of destruction of blood the patient became weak, vomited blood-streaked material, and complained of severe soreness in the left upper quadrant. The urine contained macroscopic blood, the spleen was markedly tender, and jaundice developed. Within five days after treatment was stopped, practically all symptoms had subsided and splenic tenderness had disappeared. The basal metabolic rate which was +19 at the beginning of treatment later was +37 and +27, and finally +15 at the time the patient was dismissed.

TABLE 7—*The Blood (Case 4)*

Date, 1925	Hemoglobin		Erythro- cytes, Millions	Leuko- cytes	Cells by Hemato- crit, per Cent	Blood		Plasma		Total Cir- culating Volume of Hemo- globin, Gm	Serum Bili- rubin, Mg	Total Dose of Drug, Gm	Clinical Notes
	Grams, per Cent	Per Cent				Volume, Cc	Cc for Each Kg of Body Weight	Volume, Cc	Cc for Each Kg of Body Weight				
6/20	19.4	127	6.89	9,500	71	7,700	167	2,250	48	1,490	1.5	2.0	Weight, 46 Kg Jaundice 1
6/29	19.0	123	6.90	9,000		7,800	160	2,970	63	1,480	5.3	3.4	Blood vomited, marked soreness over spleen, in- farct (?)
7/ 6	12.2	80	5.60	12,000	37	4,800	104	3,020	65	580	5.7		Jaundice 2, pallor, weak- ness, headache, vomiting, nausea
7/ 8			4.76	15,000									Recurrence of migraine attacks
7/10			1.20	16,000									
7/11	8.7	57	4.20	16,900	23	4,350	102	3,397	79	380	3.9		Spleen smaller, tender 1, 2 cm below costal margin
7/15	7.0	46	2.50	17,500									Feeling well
7/20	8.4	57	2.04	9,000	23	4,020	89	3,100	69	330			No definite symptoms
10/ 3*		130	6.60										Feeling well, weight, 56 Kg

* Courtesy of Dr John Valens, Saskatoon Saskatchewan

At dismissal the patient felt fairly strong in spite of her anemia, the symptoms had entirely disappeared. A total dose of 3.5 Gm of phenylhydrazine was given during a period of fourteen days. Four months later she wrote that she was feeling well, but had had several attacks of migraine (tables 7 and 8).

The chief complaint in this instance was of an aggravation of pre-existing migraine. The number of open capillaries for each square millimeter of skin on the back of the hand was about double the normal number. A severe hemolytic crisis occurred during treatment. Later the more constant symptoms disappeared but the attacks of migraine recurred.

CASE 5—History—A man, aged 64, entered the clinic Nov 10, 1925, complaining of pain in the right leg. Two years previously, pain, which was related to exercise, began in the muscles of the left leg, especially in the left foot and calf. Eighteen months later the left lower leg was amputated, elsewhere, on account of pain and impending gangrene. Since that time he had had severe pain in the stump, although not severe enough to prevent sleep. Similar, less severe symptoms had developed in the right leg and foot during the last year. His leg fatigued easily, and when he walked an ache developed in the ball of the foot. The foot was extremely cold for several days at a time. Bluish spots appeared on the skin. He

TABLE 8—Renal and Hepatic Function (Case 4)

Date 1925	Renal Function		Hepatic Function			Urine					
	Phenol- sulphon- phthalein, per Cent	Blood Urea, Mg	Blood Creat- inine, Mg	Dye Re- tention Grade 0 to 4	Serum Bili- rubin, Mg	Color	Bile	Uro- bilin	Grade 0 to 4		
									Albu- min	Casts	Eryth- ro- cytes Leuko- cytes
6/17	50	11	1.1	0	1.5					0	1 0
6/23	50					Dark	Trace		1	0	1 2
6/27					5.3	Dark	Trace		1	0	1 2
7/7	65	69	1.5	0	5.7	Dark	Trace	+	2	0	2 1
7/11		36	1.3		3.9	Dark			1	0	1 2
7/20	50						0	0	1	0	0 2

had been worried about his condition, fearing loss of his right foot. His father had died of a stroke at the age of 74.

Examination—The patient was fairly well preserved, and weighed 140 pounds (63.5 Kg). His face and hands were definitely red and his nose cyanotic. The mucous membranes were cyanotic and the sclerotics were injected. The heart measured 10 cm to the left, the sounds were of a good quality with a marked accentuation of the aortic second sound. The aorta was palpable in the episternal notch, and there was bilateral pulsation of the carotids. The systolic blood pressure was 204, and the diastolic 120. The spleen measured 5 cm and the liver 6 cm below the costal margin in the nipple line on full inspiration. They were firm to touch, but not tender. Pulsations were constant in the right femoral and popliteal muscles, and intermittent in the dorsalis pedis and posterior tibial muscles. The right foot was reddish blue and cold, with a sharp demarcation of the temperature line at the ankle. The circulatory efficiency tests of the right leg showed a marked bluish pallor at 180 degrees, whereas at 0 there was mild reactionary rubor. The retinal veins were moderately engorged and the arteries small and contracted. The nail-fold capillaries were long, narrow and arteriosclerotic in type, with slight engorgement of the venous limb. Roentgenologic examination of the right leg showed definite calcification of the vessels. An electrocardiogram showed no significant changes. The maximal specific gravity of the urine was 1.022. The phenolsulphonphthalein excretion was 40 per cent in two hours. There were 24.5 Gm of hemoglobin for each 100 cc of blood, the erythrocytes numbered 5,020,000,

TABLE 9—*The Blood (Case 5)*

and the leukocytes 13,000 The volume of the whole blood was 8,580 cc (136 cc for each kilogram of body weight), and the erythrocytes by hematocrit were 60 per cent The diagnosis was polycythemia vera, essential hypertension, generalized arteriosclerosis, and endarteritis obliterans of the arteries of the leg

Treatment—A total dose of 43 Gm of phenylhydrazine hydrochloride was given during a period of fifteen days The effect was definite The usual leukocytosis appeared soon after starting the drug There was a gradual reduction in blood volume of approximately 50 per cent, from 8,580 to 4,550 cc The urine became dark brown five days after the administration of the drug As the volume of blood decreased, the pain in the legs diminished Jaundice and an increase in the serum bilirubin developed No change in the size of the liver or spleen was noted during treatment The phenolsulphonphthalein output decreased to 15 per cent There was no increase in the blood urea At the time the patient was dismissed he was completely relieved from pain in the right foot and left stump He felt somewhat weak, but said he had not felt better for years The systolic blood pressure dropped to 160, and the diastolic to 90, as a result of his initial rest in bed, a further reduction occurred during treatment (systolic 130, and diastolic 70)

The points of interest in this case are (1) the evidence of endarteritis obliterans with pain out of proportion to the demonstrable vascular occlusion, (2) the hypertension of the essential type with considerable arteriosclerosis, and (3) complete relief of pain in the legs and a reduction in the hypertension with treatment by phenylhydrazine (tables 9 and 10)

TABLE 10—Renal and Hepatic Function (Case 5)

Date, 1925	Renal Function		Hepatic Function			Urine					
	Phenol sulphon phthalein, per Cent	Blood Urea, Mg	Blood Creatinine, Mg	Dye Re tention Grade 0 to 4	Serum Bilirubin, Mg	Color	Bile	Uro bilin	Grade 0 to 4		
									Albu min	Eryth ro Crsts	Leuko cytes
11/11	40	43	17	1	0.7				1		1
11/24								0	0	0	0
11/26						Dark brown		+			
12/ 1						Dark brown		+	0	1	
12/ 6	15				60			+	1		
12/11		42					Trace	+	1	1	1
12/15	15	33				Light brown					

CASE 6—*History*—A man, aged 55, entered the clinic Dec 1, 1925, with a complaint of weakness, pain and aching in the arms, shoulders, knees and lower lumbar regions, and mild nocturia and dysuria, of six or seven years' duration Tonsillectomy three years previously had afforded some relief His eyes had been somewhat bloodshot for the last three years, and his wife had noticed increasing redness of his face, especially for six or seven months Sweating was excessive in the warm weather, and the previous summer he had not been able to work because of increasing fatigue and weakness He became cold easily and warmed up with difficulty, but felt suffocated in a warm room His appetite had been excessive for several years

Examination—The patient was well nourished and robust, weighing 185 pounds (83.9 Kg) His appearance was very striking The face, neck, hands and feet were markedly cyanotic The mucous membranes were markedly reddish blue and the conjunctiva of the sclerotics was fiery red The skin over the entire body was moist and soft The heart measured 9.5 cm to the left, the arch 6 cm, the

TABLE 11—*The Blood (Case 6)*

Date, 1925	Hemoglobin		Erythro- cytes, Millions	Leuko- cytes	Rela- tive Vis- cosity (Hess)	Cells by Hemato- crit, per Cent	Blood		Plasma		Total Cir- culating Volume of Hemo- globin, Gm	Serum Bili- rubin, Mg	Total Dose of Drug, Gm	Clinical Notes
	Grams, Per Cent	Per Cent					Volume, Cc	Cc for Each Kg of Body Weight	Volume, Cc	Cc for Each Kg of Body Weight				
12/ 2	25.2	166	6.04	9,900	11.4			14,700	180	3,670	46	3,700		Weight, 84 Kg, cyanosis 3 of face and hands
12/ 8	26.0	171	7.00	10,200	7.5									
12/18	21.0	138	5.18	12,100								7.6	4.2	Jaundice 2
12/22	14.0	92	5.00	16,500	6.0	43		6,940	90	3,950	52	970	5.3	Jaundice 2, pallor 2 Superficial phlebitis of both legs
12/24	12.5	82	4.96	2,100										Jaundice 1, weakness, skin itchy
12/28 1926	11.0	72												Spleen much reduced in size, pallor 2
1/ 4	8.0	52			3.1	24		5,650	75	4,200	57	450	1.8	

sounds were normal The systolic blood pressure was 140, and the diastolic 100 The lower lumbar spine showed a fixation of about 80 per cent, with some localized tenderness The spleen measured 4 cm below the costal margin in the anterior axillary line The liver measured 4.5 cm below the costal margin in the nipple line The specific gravity of the urine was normal, but there was a moderate amount of albumin and occasional erythrocytes in the urine, the phenol-sulphonphthalein excretion was 40 per cent in two hours The blood urea was 18 mg for each 100 cc The Wassermann reaction was negative The hemoglobin was 166 per cent by the acid hematin method, the erythrocytes numbered 6,040,000, and the leukocytes 9,900 The volume of the whole blood was 14,700 cc (180 cc for each kilogram of body weight), the erythrocytes by hematocrit were 75 per cent The relative viscosity of the whole blood was 14.4 The retinal veins were considerably distended Roentgenograms did not show arteriosclerosis of the vessels of the leg, there was slight arthritis of the knee joints The nail-fold capillaries were engorged, the flow was slow, and there were many open capillaries The diagnosis was polycythemia vera and chronic infectious arthritis of the hypertrophic type (tables 11 and 12)

TABLE 12—Renal and Hepatic Function (Case 6)

Date, 1925	Renal Function		Hepatic Function			Urine					
	Phenol- sulphon- phthalein, per Cent	Blood Urea, Mg	Blood Creat- inine, Mg	Dye Re- tention Grade 0 to 4	Serum Bili- rubin, Mg	Color	Bile	Uro- bilin	Grade 0 to 4		
									Albu- min	Cast	Eryth- rocytes Leuko- cytes
12/ 3	40	18		0					3		2 1
12/ 8	25										
12/11									2	1	0 1
12/14	15										
12/16						Dark	++	+	2		0 1
12/17		45	1.4		7.6						
12/23	35	73	1.7								
12/28		73		0		Less dark					

Treatment—The patient received a total dose of 5.4 Gm of phenylhydrazine hydrochloride during a period of eighteen days During the height of destruction of blood he complained of dull continuous pain in both lower legs, which was due to superficial phlebitis There was no rise in temperature The redness and pain subsided after ten days, leaving the veins like hard fibrous cords Pathologic examination of a resected segment of vein revealed a subacute venous thrombosis Serum bilirubin was increased after four days of treatment, and definite clinical jaundice appeared after 4.2 Gm of the drug had been given Leukocytosis and a rapid decrease in the hemoglobin and erythrocytes followed the administration of 5.3 Gm The hemoglobin decreased 30 per cent after the drug was stopped There was an increase in the blood urea and slight diminution of the phenol-sulphonphthalein excretion The patient felt weak during the period of destruction of blood but there were no other untoward symptoms The spleen showed no change in size or tenderness The urine became dark on the fourth day of treatment, and was slightly dark at the time of the patient's dismissal The pain in the joints disappeared under treatment

This case is an example of extreme manifestations of the disease The volume of the whole blood was very high, 14,700 cc However, a total dosage of only 5.4 Gm of phenylhydrazine hydrochloride was necessary to bring about a very marked reduction in the blood volume and improvement of the symptoms Arthritis was present with pains in the joints, the pain disappeared during treatment

TABLE 13—*The Blood (Case 7)*

Date, 1925	Hemoglobin		Lympho- cytes, Millions	Leuko- cytes	Rela- tive Vis- cosity, (Hess)	Cells by Hemato- crit, per Cent	Blood		Plasma		Total On- culating Volume of Hemo- globin, Gm	Sero- rum Bili- rubin, Mg	Total Dose of Drug, Gm	Clinical Notes
	Grams, per Cent	Per Cent					Volume, Cc	Cc for Each Kg of Body Weight	Volume, Cc	Cc for Each Kg of Body Weight				
2/ 6	19.0	125	5.49	7,700		58	8,350	112	3,500	17	1,580	1.7	1.5	Spleen enlarged 1, face red 1
2/ 9	19.0	125			10.4									Weight, 73 Kg, urine, dark brown
2/23			5.93	9,900										
2/26	16.0	105	4.09	7,400		40	6,820	93	4,090	56	790	3.0	2.7	Jaundice 1, skin itching
3/ 2	11.6	76	2.73	13,600								4.8	3.6	Pallor 2, jaundice 1, dis
3/10	6.5	42	2.02	13,300	3.5	23	6,150	84	4,710	65	100	1.41	4.5	appearance of pain in legs
3/11	8.5	51	2.26	12,600										Feeling well, appetite in- creasing, no symptoms
3/17	8.6	56	2.49	12,100								0.13		
3/22			2.52	11,200										
3/23			2.56	9,200										
1926														
1/ 6*	21.4	140	5.52	9,600	10.6	64	9,390	129	3,360	16	1,996	0.8		Weight, 72 Kg

* Course of phenylhydrazine (total of 4.5 Gm) during June, 1925

CASE 7—History—A man, aged 58, came to the clinic complaining of weakness in the legs of seven or eight years' duration. The symptoms first began after standing five or ten minutes. Later, walking and cold aggravated the condition. He had had slight dyspnea on exertion and ringing in the left ear for two years. He had always had a high color, but this had been more noticeable in the last five years.

Examination—The patient weighed 165 pounds (74.8 Kg). His face, neck and hands were very red, his feet and scrotum less red. The mucous membranes were slightly cyanotic, and the tip of the nose markedly so. The spleen was just palpable. The retinal veins were full and the arteries showed fibrosis. Roentgenologic examination of both lower legs showed marked arteriosclerosis of the vessels. The urine was not abnormal and the phenolsulphonphthalein excretion was 50 per cent, while the blood urea was 26 mg. The systolic blood pressure was 172, and the diastolic 106. There were 19 Gm of hemoglobin for each 100 cc of blood, the erythrocytes numbered 5,490,000, and the leukocytes 7,700. The relative viscosity of the whole blood was 10.4. The total blood volume was 8,350 cc (112 cc for each kilogram of body weight). The red cell volume was 58 per cent by hematocrit. The diagnosis was polycythemia vera, mild essential hypertension with arteriosclerosis, and endarteritis obliterans incomplete of both feet.

TABLE 14—*Renal and Hepatic Function (Case 7)*

Date	Renal Function		Hepatic Function			Urine					
	Phenol sulphon phthalein, per Cent	Blood Urea, Mg	Blood Creat- inine, Mg	Dye Re- tention Grade 0 to 4	Serum Bili- rubin, Mg	Color	Bile	Uro- bilin	Grade 0 to 4		
									Albu- min	Eryth- ro Casts	Leuko- cytes
2/ 6	50	26							0		1
2/19		40	20		17	Brown	0	0	1	0	0
2/20						Dark	0	0	0	0	1
2/25	60	46	14		37	brown	+	+	0	0	0
3/ 3	75	63	28	0	48	Very dark	+	+	0	0	0
3/ 8					30		+	+	0	0	0
3/10		35	20		14				0	0	0
3/14		17	15			Normal			0	0	0
3/17					0.13		0	0	0	0	0
1926											
1/ 7*	50				0.8				0	0	0

* Course of phenylhydrazine (total of 45 Gm) during June, 1925

Treatment—A total dose of 45 Gm of phenylhydrazine was given over a period of eight days. The total blood volume became reduced to 6,800 cc (93 cc for each kilogram of body weight), and the hemoglobin to 11.6 Gm per cent. The number of erythrocytes fell to 2,730,000, and the leukocytes rose to 15,600. There was an increase of serum bilirubin to 48 Gm during the peak of blood destruction, slight jaundice appeared but no severe hemolytic crisis occurred. No change in hepatic function was demonstrated by the dye test. Further destruction of the cells continued for six days after the cessation of treatment, the blood dropping to 6.5 Gm of hemoglobin per cent, and the erythrocytes to 2,020,000. Moderate leukocytosis continued, the leukocyte count varying from 11,000 to 13,300. Regeneration of the blood began ten days afterward. At the time of dismissal the patient was much improved. Six months later there was a slight return of symptoms and he then took a subsequent course of 45 Gm of phenylhydrazine hydrochloride. The effect of this course of treatment was not so marked, although relief from symptoms was complete. The patient returned to the clinic six months later, one year after his first admission. At this time his hemoglobin was 21.4 Gm per cent. The erythrocytes numbered 5,520,000, and the leukocytes 9,600. The total blood volume was 9,330 (129 cc for each kilogram

of body weight), the relative viscosity was 10.6. The platelets were slightly increased in number, the renal function was 50 per cent, and the serum bilirubin was 0.8 mg. There had been no weakness of the legs, and the man was able to carry on his work as well-driller without undue fatigue. His facial color was distinctly red, the skin capillaries showed the usual engorgement of the venous segment, and there was a marked increase in the number of visible capillaries. A third course of 4.5 Gm of phenylhydrazine was given with satisfactory result (tables 13 and 14).

The volume of the whole blood was not high in this case, and some of the symptoms were apparently due to endarteritis obliterans. Distress and weakness in the legs were complained of rather than actual pain, but these symptoms disappeared with treatment and reduction in the volume of the blood.

SUMMARY AND COMMENT

Phenylhydrazine, first used in the production of experimental anemia in animals, has been administered to patients with polycythemia vera because of its specific effect in the destruction of erythrocytes. Given

TABLE 15—*Average Amount of Hemoglobin Destroyed by Phenylhydrazine Hydrochloride*

Case	Weight, Kg	Total Circulating Hemoglobin Destroyed, Gm	Total Dose of Phenylhydrazine Hydrochloride, Gm	Hemoglobin Destroyed,* Gm
1	60	1,800	7.6	4
2	68	3,000	6.4	7
3	67	3,340	6.0	8
4	46	1,150	3.4	7
5	63	1,700	4.2	6
6	84	3,200	5.3	7
7	73	1,180	4.3	3
Average	65.8	2,200	5.7	6

* Calculated according to the Dye method on the basis of kilograms of body weight, by each gram of drug.

subcutaneously in animals it was shown to be very toxic, but given by mouth to patients its toxicity seems to be low. Recent experiments have also demonstrated that when the drug was given by mouth to the experimental animal, the toxicity was much lower. Acetyl phenylhydrazine is being used experimentally because of evidence which points to a still lower toxicity.

In the complete clinical and physiologic studies in seven cases of polycythemia vera treated by phenylhydrazine reported, the effect of phenylhydrazine on destruction of blood and the reduction of erythrocytes is definite, constant, and specific, and gives symptoms indicative of a hemolytic crisis. An increase in leukocytes is stimulated even by small doses of phenylhydrazine, and this stimulation is specific. The platelet count does not seem to be appreciably affected. The effect of the drug on destruction of blood was evident for from

seven to ten days after its discontinuance, and this observation should be taken into account in the practical use of the drug. The marked reduction in the volume of the blood and the symptomatic improvement accompanying it were most striking. The reduction in blood volume seemed to be directly proportional to the destruction of erythrocytes, and when anemia had been produced, a relative increase in the plasma volume was observed. Jaundice appeared early during treatment and was accompanied by an increase in the serum bilirubin. The bromsulphalein test showed no dye retention during treatment, the fructose tolerance test revealed no demonstrable change. The phenol-sulphonphthalein test showed slight retention of the dye in three cases, although this may have been due to an inaccuracy caused by the dark urine, in instances in which the urine was cleared higher values were obtained. Chemical studies of the blood showed very marked elevation of the blood urea and slight elevation of the creatinine during treatment. The blood urea curve, however, followed the course of destruction of blood and was evidently due chiefly to the excessive destruction of cells rather than to retention, although a certain degree of retention may have been caused by an excessive amount of hemoglobin and its derivatives, in the tubules of the kidney, as suggested by the findings of Baker and Dodds¹⁵. Thrombosis occurred during the period of active destruction of blood in three cases: in one it followed an intravenous injection, in one it occurred spontaneously in the superficial veins of the left leg, and in another symptoms somewhat suggestive of infarction of the spleen were present. Thrombosis is seen in cases of polycythemia vera when no treatment is being given, nevertheless its occurrence during treatment by phenylhydrazine demands further consideration. Specific bacterial infection at a time of decreased resistance and the liberation of an excess of thromboplastic material as a result of the destruction of erythrocytes and possibly platelets are factors to be studied.

Following treatment the clinical improvement was satisfactory in all but one case in which marked hypertension persisted. Vertigo, fulness of the head, neuralgia, weakness and mental irritability all disappeared. Patients who had had pain in the legs claimed complete relief. A gradual increase in the erythrocytes and volume of blood necessitated a second course of treatment, in from three to six months after the first course. As a rule, the dose effective at the time of the first treatment was equally effective in the recurrences. This was especially true in one case in which, during the third course of treatment, destruction of blood was apparently just as active as during the first course on the same dosage. One or two doses of the drug each week, or a short course each month,

15 Baker S. L., and Dodds E. C. Obstruction of Renal Tubules During Excretion of Hemoglobin. *Brit J Exper Path* 6: 247-260 (Oct) 1925.

may prove effective in maintaining an approximately normal condition. Our patients have been able to determine for themselves by their symptoms when further treatment was required.

Particular attention should be directed to the cases in which there was pain in the legs apparently due to calcification of the arteries. The excellent results in these cases suggest that the drug may be beneficial in cases of endarteritis obliterans without polycythemia.

The drug was given in doses of 0.10 Gm. three times a day, the total amount given varied from 3.4 to 7.6 Gm., the average total being 5.7 Gm. It was estimated that each gram of phenylhydrazine brought about the destruction of an average of 6 Gm. of hemoglobin. It has been found wise to discontinue the use of the drug when the erythrocytes drop to 4,500,000, and it is estimated that destruction of blood will continue for approximately a week longer.

Phenylhydrazine hydrochloride, in general, causes more consistent improvement in the symptoms and a more constant reduction in the blood volume than either radiotherapy or venesection. The questions involved in the occurrence of thrombosis during treatment and the ultimate toxicity of the drug, especially on the liver, can only be decided by more extended experience and more prolonged observation.

THE PATHOGENESIS OF LIPOID NEPHROSIS *

HERMAN ELWYN, M D

NEW YORK

I

Lipoid nephrosis is a disease characterized by an insidious onset, a chronic course, edema, oliguria, albuminuria, changes in the protein and lipoids of the blood, and the deposit of lipoids in the kidney. It occurs alone, or in combination with diffuse glomerulonephritis, or with amyloid degeneration of the kidney.¹

The disease thus characterized has gradually won for itself a place as a distinct clinical entity as a result of the work of numerous investigators during the last fifteen years. It is desirable to follow some of the steps in this development. The disease was formerly included under the term of chronic parenchymatous nephritis or the large white kidney. When one reads the description of chronic parenchymatous nephritis in Senator's² work on diseases of the kidneys, it is evident that under this term are included the diseases that we have at present learned to separate into lipoid nephrosis and some of the forms of chronic diffuse glomerulonephritis. For the purpose of separating the inflammatory diseases of the kidney from the purely degenerative, Muller³ in 1905 proposed the term nephrosis for the latter. Such a separation was at that time a purely pathologic one and could not be carried through clinically.

In 1907 appeared Loehlein's⁴ work on the inflammatory diseases of the kidney. It showed the unity of all forms of diffuse glomerulonephritis and demonstrated that the subacute, subchronic and chronic forms are the result of a previous acute diffuse nephritis. It showed also the dependence of the pathologic changes in the tubules on those of the glomeruli.

The disease known as chronic parenchymatous nephritis presented many clinical difficulties. At times it was accompanied by a tense hard pulse, an increase in blood pressure, and cardiac hypertrophy, at other times these were absent. A step forward was made when Munk⁵

* From the Medical Service of Gouverneur Hospital.

1 Elwyn, H. Nephritis, New York, Macmillan Company, 1926, p. 186.

2 Senator, H. Die Erkrankungen der Nieren, ed 2, Vienna, A. Holder, 1902, p. 248.

3 Muller, F. Verhandlungen der Deutschen pathologischen Gesellschaft, Jena, G. Fischer, 1905, p. 64.

4 Loehlein, M. Ueber die entzündlichen Veränderungen der Glomeruli bei menschlichen Nieren und ihre Bedeutung für die Nephritis, Arb. a. d. path. Inst. zu Leipzig, 1907.

5 Munk, F. Klinische Diagnostik degenerativer Nierenerkrankungen, Ztschr. f. klin. Med. 78 1, 1913.

in 1913 attempted to separate clinically the degenerative diseases of the kidney. He found in some cases with marked albuminuria, edema and low blood pressure, the presence of double refractive lipoids in the urine and in the cells of the convoluted tubules of the kidney. In 1912-1914 Epstein⁶ published studies on blood serums and edema fluids. He found in some cases of chronic parenchymatous nephritis a reduction in the total protein of the blood, and showed that this reduction is in the albumin fraction while the globulin is increased both relatively and absolutely. He also found that the edema fluid in this disease contained little protein, as low as 0.1 per cent.

In 1914 appeared the classical monograph of Volhard and Fahr.⁷ These investigators showed that the pathologic changes in the various forms of glomerulonephritis can be correlated with the clinical phenomena. They also showed that of the degenerative changes in the tubules, for which the term nephrosis was used by Muller, one form, that of lipid degeneration, corresponded to a definite clinical picture. Volhard gave a classical clinical description of this form which he called "genuine nephrosis" or chronic nephrosis. This form corresponds to the definition at the beginning of this article and has a clinical picture totally different from the other forms of tubular degeneration or nephrosis. It was necessary, if the term nephrosis was to remain generic for all forms of tubular degeneration, to have a special designation for the genuine nephrosis in which lipid degeneration in the kidneys and lipid changes in the blood are important features. Munk⁸ proposed the term lipid nephrosis. This term has been accepted by most writers on the subject.

Further advance in this disease was made by studies on the protein and cholesterol content of the blood, by studies on the basal metabolism, by the introduction of the high protein diet by Epstein⁶ and of thyroid extract by Eppinger⁹ in the therapy of this disease. Numerous case reports have appeared in the literature, so that at the present time the disease constitutes a distinct clinical and pathologic entity.

Of the numerous problems that call for solution in this disease, none is of such absorbing interest as that of the pathogenesis. Before discussing this, I shall review briefly the essential clinical features.

6 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, *Am J M Sc* **154** 638 (Nov) 1917.

7 Volhard and Fahr. *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

8 Munk, F. *Die Nephrosen*, *Med Klin* **12** 1019 (Sept 24) 1916.

9 Eppinger, H. *Pathologie und Therapie des Odems*, Berlin, Julius Springer, 1917.

II

The disease begins insidiously with loss of appetite, fatigue, pallor, and edema of the ankles. In some cases the onset is definitely dated from an attack of acute diffuse glomerulonephritis or from a pregnancy. Examination of the urine shows the presence of albumin. The other symptoms then make their appearance.

The urine is diminished in amount to as low as a few hundred cubic centimeters daily, for long periods of time. It contains large amounts of albumin, 5, 10 and 20 grams per liter, as much as 60 Gm per liter has been recorded. The specific gravity is high and may reach 1.050. In the sediment are found hyaline and granular casts, leukocytes and epithelial cells, some of which contain lipoids. Doubly refractive lipoids are also found as free granules.

The edema appears first in the ankles or in the eyelids and spreads gradually. It involves the skin and subcutaneous tissue and follows the law of gravity, being found more in the dependent parts. The serous cavities are involved. The edema may involve the gastro-intestinal tract and cause diarrhea.

The blood changes affect the proteins and the lipoids. Myers¹⁰ gives the following figures for the normal protein content of the blood: for the total serum protein, 6.5 to 8.2 per cent, for serum albumin, 4.6 to 6.7 per cent, serum globulin, 1.2 to 2.3 per cent. In lipid nephrosis Epstein¹¹ found the figures for the total protein of the blood to average 3.928 per cent and the ratio of albumin to globulin to average 0.466 per cent of albumin to 3.426 per cent of globulin. Linder, Lundsgaard and Van Slyke¹² record the lowest figure for the protein in nephrosis as follows: albumin, 0.75 per cent, globulin, 2.84 per cent, total serum protein, 3.60 per cent. They conclude that the reduction is in the albumin fraction, and that the globulin is either normal or slightly increased. Fibrinogen was found to be increased by Kollert and Starlinger¹³ and by others. The rate of sedimentation of red blood corpuscles is increased.

The cholesterol in the blood is increased. Normally it is 0.21 per cent, according to Bloor. In lipid nephrosis figures as high as 1.3 per cent have been found by Epstein, up to 0.928 per cent by Schwarz and

10 Myers, V. C. Chemical Changes in the Blood and Their Clinical Significance, *Physiol. Rev.* **4**: 279 (April) 1924.

11 Epstein, A. A. Further Observations on the Nature and Treatment of Chronic Nephrosis, *Am. J. M. Sc.* **163**: 167 (Feb.) 1922.

12 Linder, G. C., Lundsgaard, C., and Van Slyke, D. D. The Concentration of the Plasma Proteins in Nephritis, *J. Exper. Med.* **39**: 887 (June) 1924.

13 Kollert, V., and Starlinger, W. Albuminurie und Bluteiweissbild, *Ztschr. f. d. ges. exper. Med.* **99**: 426 (March) 1924.

Kohn,¹⁴ up to 0.730 per cent by Hiller, Linder, Lundsgaard and Van Slyke¹⁵

The blood volume is normal, which is of great significance. The total nonprotein nitrogen, urea, uric acid and creatinine are not increased in uncomplicated lipoid nephrosis. Figures slightly above normal occur, and such an increase is usually found when the edema fluid is quickly reabsorbed into the blood stream. When this occurs, the fluid entering the blood stream carries with it the nonprotein nitrogenous substances contained in the edema fluid, and thus helps to swell the total figure in the blood.

Tests for kidney function give a normal response provided the tendency to edema formation does not interfere with the tests. The basal metabolism has been found lowered in this disease by Epstein and Lande.¹⁶ They report figures as low as minus 19 per cent.

An increase in blood pressure does not occur in pure lipoid nephrosis. The heart is not enlarged. On the contrary, it is often found on necropsy to be small and atrophic.

III

When we look for the pathologic changes that underlie these clinical phenomena, we find comparatively little. In the case of an uncomplicated lipoid nephrosis we find in the kidneys lipoid infiltration in the cells of the convoluted tubules with a certain amount of hyaline degeneration, lipoid infiltration in the interstitial tissue of the kidneys, and moderate fatty degeneration of the glomeruli. It is this incongruence of the profound humoral changes with the comparatively slight anatomic findings which led many students of this disease to consider it the result of some general metabolic disorder. Munk¹⁷ sees the essence of this disease in a physicochemical change involving all the colloids of the body. Similar views are expressed by others. Such general assumptions are, however, of little value.

The etiology of many cases of lipoid nephrosis is quite obscure. They come to the notice of the physician in an advanced state, and any exciting or predisposing factors cannot be determined. Others can, however, be definitely traced to an acute diffuse glomerulonephritis which preceded the onset of the symptoms peculiar to lipoid nephrosis. Occasionally one gets the opportunity of following a case from its beginning as an acute diffuse glomerulonephritis to the full development

14 Schwarz, H., and Kohn, J. L. Studies of Nephritis in Children, *Am J Dis Child* **24** 125 (Aug) 1922.

15 Hiller, A., Linder, G. C., Lundsgaard, C., and Van Slyke, D. D. Fat Metabolism in Nephritis, *J Exper Med* **39** 931 (June) 1924.

16 Epstein, A. A., and Lande, H. Studies on Blood Lipoids, *Arch Int Med* **30** 563 (Nov) 1922.

17 Munk, F. Pathologie und Klinik der Nierenerkrankungen, ed 2, Berlin, Urban and Schwarzenberg, 1925, p 298.

of lipid nephrosis. Acute diffuse nephritis must, therefore, be considered as an etiologic factor. Lipid nephrosis is also a frequent accompaniment of the subchronic and chronic forms of diffuse glomerulonephritis. The writers who assume that lipid nephrosis is a purely metabolic disease consider the presence of a nephritis with the nephrosis as purely accidental. However, the combination of the two diseases is of such frequent occurrence that a closer relationship than accident must be granted.

Other diseases that seem to stand in some relationship to lipid nephrosis are those which lead to amyloid changes in the organs, namely, tuberculosis, syphilis and chronic suppuration. Amyloid disease is frequently found combined with lipid nephrosis.

Still problematic is the connection between pneumococcus infection and lipid nephrosis. Since Volhard¹⁸ first observed this, the termination of many of these cases by a pneumococcus peritonitis has been found to be a common occurrence. Such cases have been reported by Schwarz and Kohn,¹⁴ Bock and Mayer,¹⁹ Vandorfy,²⁰ Stolz,²¹ Fanconi²² and others. Stolz found in a case of nephrosis gram-positive diplococci in the walls of the glomerular capillaries, in the cells of the tubules, and in the intertubular capillaries. In another case he found pneumococci in the intertubular connective tissue and in the epithelial cells. Stolz is of the opinion that the pneumococcus there causes an inflammation that is at first acute, but soon takes on a chronic character, resulting in an injury to the tubules. At times the pneumococci invade the peritoneal cavity where, because of the presence of ascites, the serous cells have lost their bacteriocidal power. The repeated occurrence of pneumococcus peritonitis in these cases is certainly remarkable, and the possibility of this organism playing a rôle as an etiologic factor must be kept in mind. The organism may, however, be a secondary invader.

With these data in hand, how can we undertake the problem of the pathogenesis of this disease?

The essential elements that characterize lipid nephrosis, aside from any negative features, such as the absence of hypertension, of cardiac hypertrophy, and of renal insufficiency, are the albuminuria, the

18 Volhard, F. Die doppelseitigen Hamatogenen Nierenerkrankungen, in Mohr and Staehelin's Handbuch der Inneren Medizin, Berlin, Julius Springer, 1918, 3 1467.

19 Bock and Mayer. Ein Fall von genuiner Nephrose mit Pneumococcus Peritonitis als Ausgang, Med Klin 16 101 (Jan 29) 1920.

20 Vandorfy, J. Ein mit Pneumococcus Peritonitis verlaufender Fall von Nephrose, Med Klin 17 657 (May 29) 1921.

21 Stolz, E. Ueber die sogenannte Pneumokokkennephrose, Med Klin 18 1376 (Oct 22) 1922.

22 Fanconi, G. Zur Oedemfrage, Genuine Nephrose und idiopathisches Oedem, Jahrb f Kinderh 110 12 (Sept) 1925.

oliguria, the edema, the hypercholesterinemia, the changes in the plasma protein, the lipid deposit in the cells of the convoluted tubules, and the lowered basal metabolism. Each one of these elements has been considered by some investigator as of central interest and importance. The disease occurs either alone or in combination with diffuse glomerulonephritis or with amyloid degeneration of the kidneys.

Do all these features appear at the same time, or does one symptom appear first and the others later? Are they all concomitant results of some unknown cause, or are some of the elements the result of others in this group? The correct answer to these questions is important. From those cases which come under observation when the disease is fully developed and which cannot be traced to a definite onset we are not able to learn that which will help us in answering the first of these questions. Occasionally, however, the opportunity is given to trace the symptoms to the time of onset, or more luckily still, to observe the patient from the beginning. I have had the opportunity to observe several cases from the onset of an acute diffuse glomerulonephritis. In these cases the symptoms of the acute nephritis, namely, the edema, hematuria, the increase in blood pressure, and the evidence of renal insufficiency soon disappeared, and only the albuminuria remained. The amount of albumin in the urine was large and within six months the other symptoms of lipid nephrosis began to appear.

In the cases, therefore, which can be followed from an acute diffuse nephritis which had subsided, the first step in the development of the lipid nephrosis is the persistent albuminuria. What is the cause of this persistence of the albuminuria?

The proteins in the urine have definitely been shown to be identical with the proteins of the blood, namely, serum-albumin and serum-globulin. According to the careful investigations of Csatai,²³ the amount of globulin in the urine in parenchymatous nephritis is comparatively small and the albumin is present in many times the amount of the globulin. According to the recent investigations of Linde, Lundsgaard and Van Slyke¹² also, the albumin in the urine in lipid nephrosis is present in many times the amount of the globulin. It is evident that the proteins of the blood, and especially the serum-albumin, escape into the urine. That they thus escape by way of the glomeruli can hardly be questioned. The evidence for this is presented by Cushny²⁴ and by Richards²⁵. The reason for their escape in such large quantities without the presence of any inflammation in

²³ Senator, H. Die Erkrankungen der Nieren, ed 2, Vienna, A. Holder, 1902, p. 262.

²⁴ Cushny, A. R. The Secretion of Urine, London, Longmans, Green & Co., 1917, p. 201.

²⁵ Richards, A. N. The Nature and Mode of Regulation of Glomerular Function, *Am J M Sc* **170** 781 (Dec.) 1925.

the glomeruli is not so obvious. In the presence of such an inflammation, the diminution in nutrition, especially in oxygen supply, to the glomerular and capsular epithelium results in the injury to the cells, which increases their permeability for the proteins of the blood. This injury usually persists in most cases for some time after the inflammation in the glomeruli has subsided, and the result is a persistent albuminuria for some period after recovery from an acute nephritis. It is evidently this damage which persists in an unusual degree in those cases which eventually progress to a lipoid nephrosis. Whether such cases of acute nephritis which subside and leave a persistent injury to the glomerular epithelium have the pneumococcus as the causative agent is a problem for future investigation.

The reason that the albumin escapes in larger quantities than the globulin is probably found in the fact that it consists of smaller molecular aggregates than the globulin. Cloetta²⁶ has shown that the relative amounts of albumin and globulin, which pass through a membrane, are dependent on the density of the membrane. The more dense the latter, the less globulin passes through. This fact is of importance for our further considerations.

We have, then, as the first step in the pathogenesis of lipoid nephrosis, the escape of the proteins of the blood plasma, especially the albumin, into the urine as a result of a previous acute diffuse glomerulonephritis which has subsided but has left a more or less persistent injury to the glomerular and capsular epithelium.

V

Can we explain the other manifestations of lipoid nephrosis as a consequence of the loss of the proteins of the blood into the urine?

In the further considerations I shall take as a guide two principles that enter into the fundamentals of modern physiologic concepts.

1 The living organism continuously attempts to maintain normal values within narrow limits of variation for those substances which it needs in its economy and for those processes and activities within itself to which it has become adapted. The means that the organism uses in maintaining and regulating such values are only known in some instances, and then but incompletely. In cases in which the means are known it is evident that they are physicochemical, hormonal and nervous, with a center of control in the central nervous system. Examples are numerous, such as the maintenance and regulation of the acid-base balance, of the normal temperature, of the amount of sugar in the blood, of the rate of metabolism, and so on. The object of physiologic

26 Cloetta, M. Ueber die Genese der Eiweisskörper bei der Albuminurie, Arch f exper Path u Pharmacol 42 453 (June) 1899

investigation is always to find all the means by which such regulation is effected

2 When any loss occurs in such substances, or a disturbance in such processes or activities with a threatened change in normal values, all the means of regulation of which the organism is capable are brought into play in an attempt, whether successful or not, to maintain the normal values. Here again, examples are numerous, such as all the reactions of immunity, the healing of wounds and compensatory hypertrophy. The object of investigation in pathologic-physiologic changes is to find all the means that the organism uses in averting a threatened change, or in compensating for a change that actually has occurred.

The tendency to take these principles as a guide in the consideration of the more fundamental vegetative functions of the organism is illustrated in such discussions as that of Henderson²⁷ on the physiologic regulation of the acid-base balance, that of McLean²⁸ on edema, and that of Siebeck²⁹ on the fluid exchange.

With these principles in mind we may attempt to trace the consequences that follow the continuous loss of serum-protein, especially serum-albumin, by way of the urine. We shall attempt to view the essential elements of lipoid nephrosis as results of a disturbance in regulation, consequences of an attempt on the part of the organism to prevent the further loss of protein and to compensate for that which is already lost.

The amount of albumin lost in this manner may be very large. Senator²³ records a case in which the total amount of protein in the urine during one day was 22.4 Gm. He cites another case in which from 30 to 35 Gm. was found daily for several successive days. Epstein⁶ observed an albuminuria of several months' duration with a daily output of protein ranging from 18.5 to 26.2 Gm. That the daily loss of such large quantities of serum-albumin must necessarily reduce the amount in the blood plasma is self-evident. This was known to the older writers who spoke of a hypalbuminosis, and it has been recently emphasized by Epstein. Evidently the loss of so much plasma protein is not easily made up, which explains the low figures for the albumin and the total protein in the blood in lipoid nephrosis. It does not explain the absolute increase in the globulin fraction.

How does the organism attempt to compensate for such a loss? An attempt to compensate must be assumed if we hold to the principles enunciated above. For it is evident that the constancy of the normal

27 Henderson, Y. Physiological Regulation of the Acid-Base Balance of the Blood and Some Related Functions, *Physiol Rev* 5 131 (April) 1925.

28 McLean, F. C. Edema as a Problem in Physiological Regulation, *Physiol Rev* 5 618 (Oct.) 1925.

29 Siebeck, R. Physiologie des Wasserhaushaltes, in *Handbuch der Normalen und Pathologischen Physiologie*, Berlin, Julius Springer, 1926, 17 161.

blood protein presupposes functions which though not fully understood, must evidently be maintained

In reviewing the clinical features of lipoid nephrosis we find two elements that may be viewed in the light of an effort on the part of the organism to compensate for the loss of albumin and to prevent a greater loss. These are the increase in the plasma globulin and the diminution in the urinary output.

We have said previously that the globulin is increased not only relatively but also absolutely. This has been found by most investigators in this field. The globulin has a larger molecular aggregate and is lost in the urine in much smaller quantities than the albumin. Although it does not replace the entire amount of the lost albumin, yet we may well consider its increase as an attempt on the part of the organism to compensate for the loss of the albumin.

The diminution in the amount of urine may be viewed as an effort to prevent a greater loss of albumin by restricting the amount of fluid in which it escapes. The glomerular function that is responsible for the filtration of fluid is controlled by many factors, chemical, physical, hormonal, and from the central nervous system. It has been shown by Richards²⁵ and his associates that the number of glomeruli, and even the number of loops in an individual glomerulus, which are active at one time vary considerably, and can be made to vary by different means. In lipoid nephrosis we may, in the light of the above mentioned physiologic principles, consider the diminution in the urinary output as due to a smaller number of the glomeruli being active at one and the same time in an effort to lessen the loss of proteins from the blood.

We have then, as a second step in the pathogenesis of lipoid nephrosis, the effort on the part of the organism to restrict the loss of protein by diminishing the amount of urine, and to replace the lost albumin by an increase in the amount of the globulin, which is of a larger molecular aggregate, and which passes less easily through the injured glomerular filter.

VI

We have so far discussed the albuminuria, the oliguria, and the changes in the protein of the blood. We come now to the consideration of the edema. The explanation for the edema in this disease has always been difficult, and numerous theories have been evolved. Most of these are unsatisfactory. Usually each investigator has attempted to explain the edema on the basis of some single physical or chemical factor. Recently, Loeb³⁰ and McLean²⁸ have reviewed the problem of edema from the point of view of the regulation of the bodily fluids in the economy of the organism, and especially from the point of view of the

maintenance of the normal blood volume. In discussing the edema of acute diffuse glomerulonephritis elsewhere,³¹ I maintained that the edema there is produced in an attempt on the part of the organism to get rid of the excess of fluid in the vascular system, and to maintain the normal blood volume.

The maintenance of the blood volume within normal variations is evidently of the utmost importance to the organism. It is seldom disturbed as numerous studies on blood volume have shown, and the means of its regulation are chemical, physical, hormonal, and by the central nervous system. In lipid nephrosis the blood volume is normal, as has been shown by Linder, Lundsgaard, Van Slyke and Stillman.³² Of the forces that are concerned in the exchange of fluids in the organism, McLean mentions diffusion pressure, hydrostatic pressure, osmotic pressure and difference in electrical potential, ionic equilibrium according to the Donnan formulation, the flow of lymph, the state of the capillary membrane.

In lipid nephrosis the diminution in the amount of protein in the blood has been used to explain the formation of the edema. Epstein⁶ assumes that "the loss of protein incurred by the blood serum through the continuous albuminuria causes a decrease in the osmotic pressure of the blood, which fact favors the absorption or imbibition of fluid by the tissues." Schade and Claussen³³ designate the water-binding power of the blood proteins as the "oncotic pressure," which they do not consider to be the same as the osmotic pressure. Normally, this pressure averages 25 mm of mercury, but in patients with renal edema the figures are below 20 mm. Both the osmotic and the "oncotic" pressures may well be among the forces that the organism utilizes in the regulation of the fluid exchange. They cannot, however, be the determining factors in the edema of lipid nephrosis for at least two obvious reasons: first, variations in the extent of edema and even the absence of edema may be repeatedly observed in spite of low figures for the plasma protein, second, in spite of the low figures of the plasma protein which should lessen the entrance of fluid into the blood stream, the *normal blood volume* is maintained whatever the fluid intake might be, and whatever the variations in the extent of the edema.

I believe we must consider the problem of edema in lipid nephrosis from the point of view of an effort on the part of the organism to maintain the normal blood volume. There are two gates through which

31 Elwyn, H. Nephritis, New York, 1926, Macmillan Company, p. 110.

32 Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E. G. Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, *J. Exper. Med.* **39** 921 (June) 1924.

33 Schade, H., and Claussen, F. Der onkotische Druck des Blutplasmas und die Entstehung der renal bedingten Oedeme, *Ztschr. f. klin. Med.* **100** 363 (May) 1924.

an excess of fluid in blood can be made to escape, by way of the kidneys, and into the tissues. By way of the kidneys the escape of fluid has become difficult because of the effort on the part of the organism to reduce the loss of albumin. It is obvious that with the normal intake of fluid there will soon be an excess which must be taken up by the tissues if the blood volume is to remain normal. In the actual formation of the edema, numerous factors are concerned which are at present not sufficiently understood.

We have now, as a further step in the pathogenesis of lipid nephrosis, the formation of edema in an effort on the part of the organism to maintain the normal blood volume in spite of the reduction in the urinary output.

VII

When edema occurs as a result of cardiac failure, or with an acute diffuse glomerulonephritis, a considerable amount of plasma proteins escapes into the edema fluid. This is not the case in the edema of lipid nephrosis in which the fluid contains only about 0.1 per cent of proteins, or less. This prevention of the loss of blood protein into the edema fluid we must also consider as a part of the regulative mechanism for conserving the plasma protein. Evidently, instead of an increase in the permeability of the capillary wall, the permeability is lessened for the protein, so that water and salts only can pass through it. The mechanism by which this is effected we may conceive to lie in an *increased contraction of the capillaries*. We have some evidence for the presence of such a contraction in the marked pallor of these patients. This pallor is not due to anemia, for the red blood corpuscles and the hemoglobin are either normal in number and amount, or only moderately reduced. Krogh,³⁴ in discussing the contractility of the capillaries, cites Ebbecke "who points out the fact that redness or paleness of the human skin depends upon the quantity of blood present in the cutaneous capillaries and venules, that is, upon their state of dilatation or contraction."

A widespread contraction of the capillaries with a lessening of the amount of blood in them has as a consequence a diminution in the supply of nutrition and of oxygen to the tissues. This diminution in the nutrition causes a starvation of the tissues and organs, which is shown by the decrease in the basal metabolism, by the loss of flesh, by the lessened resistance to infection.

The diminution in the supply of oxygen results in a diminution of intracellular oxidation. Such a disturbance in intracellular oxidation Vollhard¹⁸ considers to be the cause of lipid infiltration in the kidneys.

Whenever there is an inability on the part of the cells to utilize properly their nutritive supply, lipoids accumulate in the cells and then

³⁴ Krogh, A. The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1922, p. 31.

appear in the blood. This is illustrated in the lipemia of diabetes. That a diminution in the oxidative ability causes the cells to take up lipoids is evident from the experiments of Chalataw¹⁵. He found that when the cells of the kidney tubules are poisoned by the administration of phosphorus, which inhibits oxidation, they easily take up cholesterol. The diminution in oxidation, due to the diminished blood supply to the tissues and organs as a result of capillary contraction, I consider to be the cause of the appearance of lipoids in the tissues and in the blood. By escaping through the glomerular filter the lipoids may also infiltrate the cells of the tubules, and they also appear in the urine.

I assume, therefore, that we have as a further step in the pathogenesis of lipoid nephrosis a widespread contraction of the capillaries as a result of an effort on the part of the organism to prevent the loss of plasma proteins by preventing their escape into the edema fluid. This capillary contraction results in a diminished content of blood in the capillaries as shown by the pallor of the patient. It results further in a diminished nutrition and diminished oxidation of the tissues and organs as shown by the lowered basal metabolism, the loss of flesh, and the lessened resistance to infection. The consequence of the diminished nutrition and oxidation of the tissues and organs is the appearance of lipoids in the cells, and as they accumulate they are washed into the blood stream, where their total amount is increased, as shown by the high figures for the cholesterol. The lipoids pass through the glomerular filter into the urine.

VIII

We have used as a starting point for our comment the cases of lipoid nephrosis in which the development of the disease can be followed from the onset with an acute diffuse nephritis. In the cases in which the onset is not observed, but in which the symptoms can be traced back to an attack of acute nephritis that has subsided, the same manner of development may be assumed. In the course of chronic diffuse glomerulonephritis repeated attacks of acute nephritis occur, as I have pointed out elsewhere. Each of these acute attacks may then be considered as the starting point for the possible development of a lipoid nephrosis, which then accompanies the course of the chronic nephritis.

The cases that accompany amyloid degeneration have as their etiologic factors the diseases that are responsible for the deposit of amyloid, namely, tuberculosis, syphilis and chronic suppuration. In these diseases we must assume that their toxins injure the glomerular and capsular epithelium more or less persistently. This is then followed by albuminuria, and the continuous loss of large amounts of protein

35 Chalataw, S. S. *Die Anisotrope Verfettung im Lichte der Pathologie des Stoffwechsels*, Jena, G. Fischer, 1922, p. 117.

initiates the regulative and compensatory measures that result in the eventual development of the full clinical picture of lipid nephrosis

We thus have come to the conclusion that the first symptom of lipid nephrosis is the result of an injury to the glomerular and capsular epithelium. This injury is the result of a previous acute diffuse glomerulonephritis, which has subsided, or of the toxins of chronic diseases, such as tuberculosis, syphilis and chronic suppuration. Such injury is present for a variable period in practically all cases of acute nephritis in which recovery has been made. This is evident from the persistence of a small amount of albumin in the urine for a variable period of time. Why such injury is more severe in some cases, resulting in the continuous loss of large amounts of plasma protein, is unanswerable at the present time. Perhaps such a severe injury occurs only in those cases in which the pneumococcus is responsible for the acute nephritis.

SUMMARY

- 1 The main features of lipid nephrosis are albuminuria, oliguria, edema, diminution in the total protein of the blood with a diminution in the albumin fraction and the relative and absolute increase in the globulin fraction, increase in the cholesterol of the blood, lowering of the basal metabolic rate, a practically protein-free edema fluid, and the deposit of lipoids in the cells of the kidney tubules

- 2 The disease occurs either alone or in combination with diffuse glomerulonephritis or with amyloid disease

- 3 The first symptom in the cases that can be observed from the beginning is the albuminuria

- 4 The albuminuria is the result of a more or less persistent injury to the glomerular and capsular epithelium by a previous acute diffuse nephritis that has subsided. When lipid nephrosis accompanies amyloid degeneration the injury to the glomerular and capsular epithelium is caused by the toxins of the diseases that are responsible for the amyloid deposit

- 5 The oliguria is the result of a regulative effort on the part of the organism to prevent the loss of protein

- 6 The absolute increase of the globulin fraction in the blood is the result of a regulative effort on the part of the organism in an attempt to conserve the proteins of the blood by replacing the lost albumin with a protein of a larger molecular aggregate, hence one that passes less easily through the injured glomerular filter

- 7 The edema is the result of a regulative effort on the part of the organism in an attempt to maintain the normal blood volume. Since one of the gates by which the excess of fluid is eliminated, namely, the

kidneys, is less active, there is danger that the fluid volume of the blood will be increased. This is obviated by the formation of edema.

8 To prevent the escape of the plasma protein into the edema fluid, the capillaries become less permeable by increased contraction. The result is pallor, and a diminution in the supply of nutrition and of oxygen to the tissues and organs.

9 This diminution results in a disturbance of intracellular oxidation and of the proper utilization of foodstuffs.

10 The result is a lowered metabolic rate, loss of flesh, and a diminished resistance to infection.

11 The diminution of the utilization of nutrition also results in an increase of lipoids in the cells, and later in the blood, with the production of a hypercholesterinemia.

12 The lipoids of the blood pass through the injured glomerular filter and from the filtrate add themselves to the lipoids already present in the cells of the kidney tubules. They also appear in the urine.

13 The main features of lipid nephrosis are thus considered from the point of view of regulation in an effort on the part of the organism to compensate for the loss of protein and to prevent a greater loss.

14 The possibility that the pneumococcus may be a causative factor in the production of the acute nephritis that precedes the development of lipid nephrosis must be considered. Its continued presence in the kidney, as found by Stolz, is possibly responsible for its occasional invasion of the peritoneal cavity, and the development of peritonitis.

EPIGASTRIC PULSATION

THE DIAGNOSIS OF THE ARRHYTHMIA CORDIS THROUGH THE EPIGASTRIOGRAM *

NOBUTATSU FUKUI, M D

TOKYO

Before discussing the diagnosis of arrhythmia cordis through the epigastriogram, I should like to describe briefly the study of the epigastric pulsation, which we have been investigating since the year before last ¹

The movement of the heart can be recorded at the epigastric region directly under the processus xyphoideus of the individual not only with the visible or palpable epigastric pulsation, but also, by certain methods without the pulsation. We have named this tracing "epigastriogram" or "epigastriocardigram."

I first studied the analysis of the epigastriogram through simultaneous tracings with several polygrams, i. e., abdominal aorta, radial, carotid, apex beat, jugular, hepatic pulse and also esophagocardiogram. The analysis of the epigastriogram reveals the following components: the wave a due to the contraction of the right auricle, the wave s' due to the vibration of the ventricular muscle in the beginning of the ventricular systole and then the systolic valley s, the wave d due to the ventricular diastole, and the wave c simultaneous with the pulsation of the abdominal aorta.

We studied the various forms of the epigastriograms in several diseases, especially in diseases with visible pulsations, for instance, pulmonary emphysema, beriberi, anemia, morbus Basedowii and various valvular lesions of the heart and also in asthenic constitution, and classified them as shown in the figure 1.

Then I investigated the application of the epigastriogram in the diagnosis of irregular pulse.

THE DIAGNOSIS OF IRREGULAR PULSE BY THE EPIGASTRIOGRAM

The cause of waves a, c and d in the epigastriogram is somewhat different from that of waves a, c and v of the jugular vein. In the first place the wave a of the former has its origin in the direct influence of the right auricular contraction on the epigastrium, while the wave a of the latter is caused by the transmission of the increase of the pressure of the right auricle. Second, the wave c of the former is caused by the direct transmission of the pulsation of the underlying abdominal aorta,

* From the Medical Institute of Tokyo Imperial University

1 Fukui N. On the Epigastric Pulsation, *Acta scholae med univ imp*, Kyoto 7 41, 1924

while that of the latter is assumed to be due to the carotid pulsation or again to have its origin in the shut impulse of the atrioventricular valve. Third, the wave *d* of the former is caused by the change of the position of the heart in the beginning of diastole and is sometimes followed by two or three little waves, while the wave *v* of the latter has relation to the systole and diastole of the ventricle.

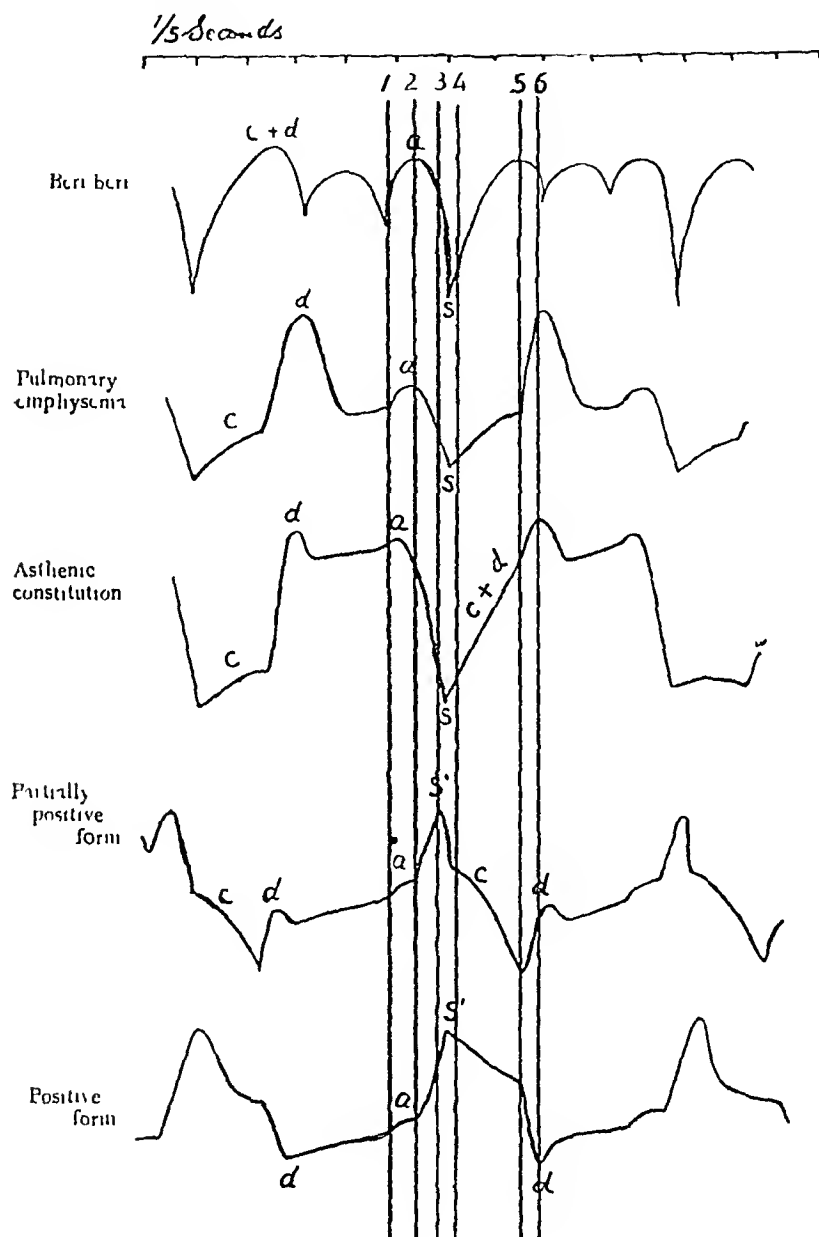


Fig 1—Several forms of epigastriograms. The perpendicular lines represent the time of the following events: (1) the beginning of the auricular systole, (2) the beginning of the ventricular systole, (3) the appearance of the pulse in the carotid, (4) the appearance of the pulse in the radial, (5) the closing of the semilunar valves, and (6) the opening of the tricuspid valves.

On the other hand, these waves of the epigastriogram can be regarded as similar in their nature to those of the jugular vein on account of the fact that the waves *a* both indicate the contraction of the right auricle

and the waves c both coincide with the arterial pulsation, though there is a minimal difference of time between the abdominal aorta and the carotid. This is the reason why we intended to substitute the epigastriogram for the venous pulse in the diagnosis of arrhythmia cordis. The recording of the jugular vein is difficult or often impossible, on account of the anatomic relationship of the regio colli. In my former report, the epigastriogram was compared with the venous pulse of the jugular vein in the diagnosis of the disturbance of atrioventricular conduction and of extrasystolic contraction and was assumed to be able to take the place of the venous pulse. In this article the epigastriogram is recorded simultaneously not merely with the jugular vein but also with the electrocardiogram, and the analysis of the epigastriogram and its clinical application are considered as to its correctness. Some cases of them will be reported as follows.

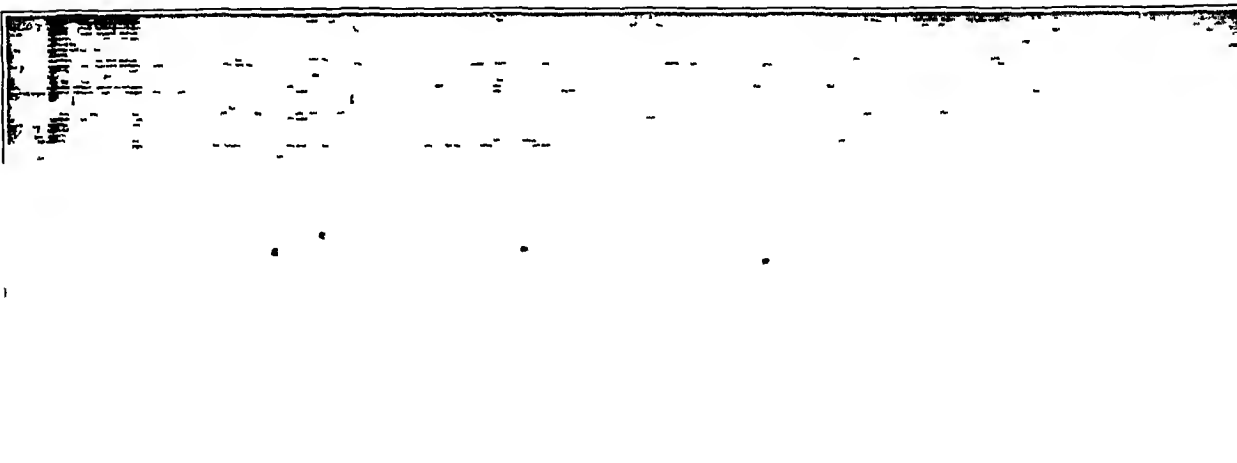


Fig 2 (case 1) —Simultaneous electrocardiogram and radial record from a case of disturbance of atrioventricular conduction, showing the correspondence of the waves a, c and d, respectively, with the peaks P, R and T.

REPORT OF CASES

CASE 1 —*Mitral insufficiency and disturbance of atrioventricular conduction*

When a woman, aged 18, was being treated with digitalis for heart insufficiency, her pulse became slow and irregular. In the electrocardiogram of figure 2, the peak P, which indicates the auricular contraction, appears at regular intervals, but R and T are often missing and sometimes P and R appear almost at the same time. The epigastriogram shows the waves a, c and d, respectively, corresponding with P, R and T, especially where P and R coincide, the waves a and c appear combined, and where R and T are missing and P appears independently, there is only an upheaval of the wave a.

Here must also be mentioned the form of the epigastriogram of this patient. The epigastriogram has a very tall upheaval of the wave a. The patient has an enormously dilated and hypertrophied right ventricle, the limits of which reach the right mammillary line, according to orthodiagraphy. This fact is the real cause of the high upheaval of the wave a as was already remarked in the former report. The epigastriogram of beriberi with hypertrophy and dilatation of the

right heart represents always a high upheaval of the wave a, especially in a severe case. Valvular failure also shows an epigastriogram similar to that of beriberi, when the right heart is dilated and hypertrophied as in the case of this patient. The jugular venous pulse indicates a very low wave (r) and the comparison of these waves (a) in the epigastriogram and the venous pulse is quite interesting. When the dilatation of the right heart of this patient was found by orthodiagraphy to have been reduced through treatment, the wave a of the epigastriogram became remarkably low and the form of the epigastriogram approached to the normal form, as is demonstrated in figure 3.

CASE 2—*Parkinsonism and auricular extrasystole*

The electrocardiogram of a man, aged 28, in figure 4 indicates the peak P, which often appears previous to the normal period. The time of the atrio-ventricular conduction is normal and P is regularly followed by R and T. The normal sinus irritation is not disturbed by the retrograde conduction of the stimulation of auricular extrasystole and thus the auricular extrasystole is followed by the normal sinus rhythm. The comparison of the epigastriogram with the electrocardiogram reveals the fact that the waves a, c and d coincide with the peaks P, R and T, respectively, and also that at the part where T is missing in the electrocardiogram, the wave d is reduced or missing in the epigastriogram.

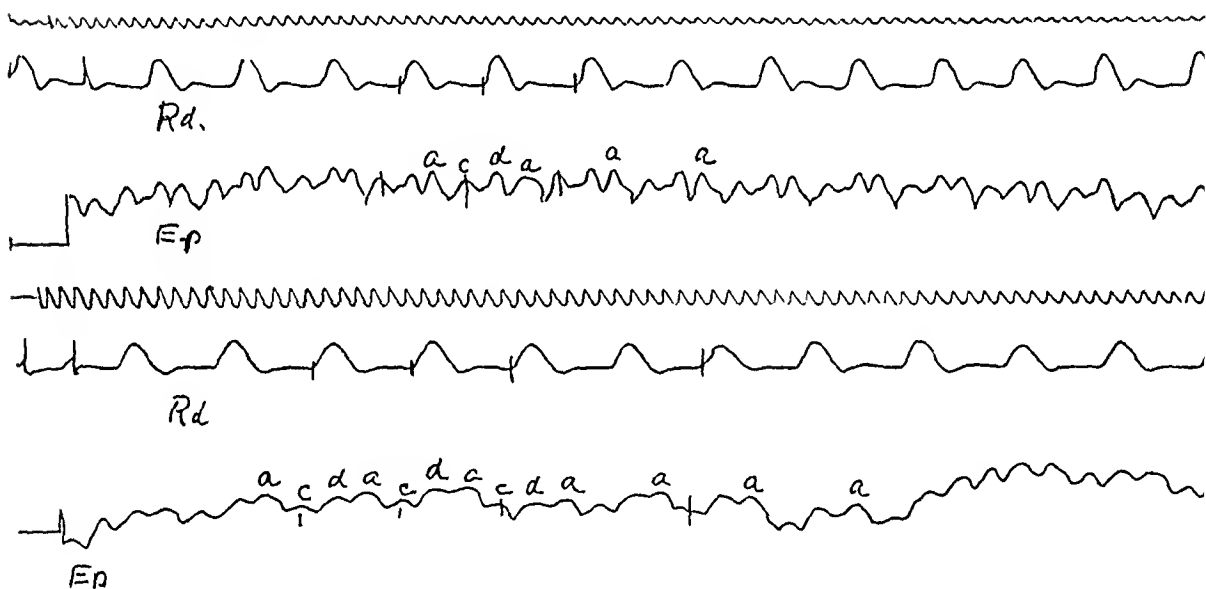


Fig 3 (case 1) —Epigastriogram made when the hypertrophy and dilatation of the right heart was reduced through treatment, showing a remarkable lowering of the wave a as compared with that of figure 2

The form of the epigastriogram of this patient indicates the form of the asthenic constitution. This patient has a paralytic chest and the limits of dulness and the sound of the heart are normal. The jugular vein represents the same diagnosis as the epigastriogram and electrocardiogram.

CASE 3—*Mitral stenosis and insufficiency and auricular flattening*

The electrocardiogram of a man, aged 23, in figure 5 shows a quite irregular feature and the auricular peak flattens with the frequency of about 250 times a minute. Now through comparison of the electrocardiogram and the epigastriogram it can be easily understood that the wave a of the latter flattens according to the flattening of the peak P of the former and in some intervals even the number of auricular flattening waves strictly coincide in both curves. On the contrary the jugular vein of this patient represents only the waves c and v, the wave a being missing in most parts.

The epigastriogram of this patient has a quite specific form, which is named positive epigastriogram. While the normal, i. e., negative epigastriogram consists of systolic retraction and diastolic swelling, the positive form swells in systole and retracts in diastole, so that the systolic valley of the negative form is trans-

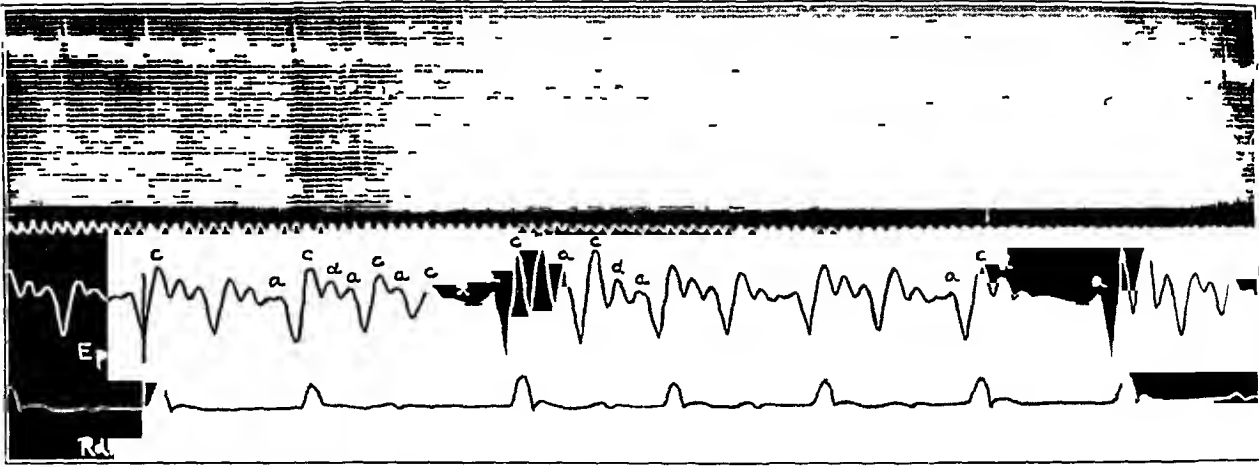


Fig 4 (case 2) —Simultaneous electrocardiogram and epigastriogram and the radial record from a case of auricular extrasystole, showing the correspondence of the waves a, c and d respectively, with the peaks P, R and T, especially where (\\) the peak T is missing, there (\\) is no wave (d). This epigastriogram reveals the asthenic constitution according to the classification of figure 1.

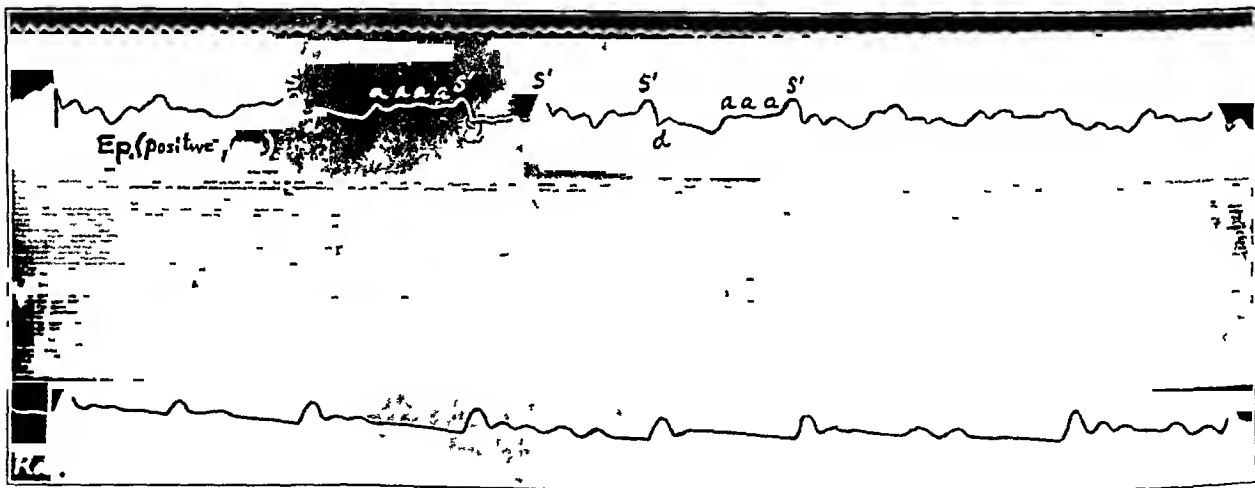


Fig 5 (case 3) —Simultaneous electrocardiogram and epigastriogram and the radial record in auricular flattening, showing the synchrony of the flattening of the wave a and the peak P. This epigastriogram belongs to the positive form, according to the classification of figure 1.

formed into a peak (s'), in which the wave c is included, as if it lies in the depth of the valley s in the negative form. The contraction of the right auricle is expressed in most cases as the positive wave, but the negative wave a is not rarely recorded. Mackenzie² took the positive form of the epigastric pulsation

² Mackenzie, J. The Study of Pulse, 1902, p. 37.

for the sign of hypertrophy of the left heart, but his opinion is not always acceptable in view of my observation of many cases since the year before last on account of the fact that the positive form is often recorded in the epigastric pulsation without hypertrophy of the left ventricle. As for this case, the heart is enlarged to the right and left and the apex beat is remarkably strong.

CASE 4—*Contracted kidney and auricular fibrillation*

In the electrocardiogram of a man, aged 68, in figure 6, P is missing and the interval is very irregular, while the relation between R and T is normal. The epigastrigram has the wave c and d, but no a and in some parts a slight prominence is seen which looks like wave a. This slight prominence *s'* is named the partially positive form, which is shaped by the transformation of the forepart of the systolic valley into the positive wave as is shown in figure 1. This wave is often recorded in the subject with the heart intact and is sometimes mistaken for the wave a, because it appears directly after the auricular wave. The high prominence of the wave d in this epigastrigram is quite characteristic of pulmonary emphysema according to the classification of figure 1 and the epigastrigram of the aged is chiefly recorded in this type.

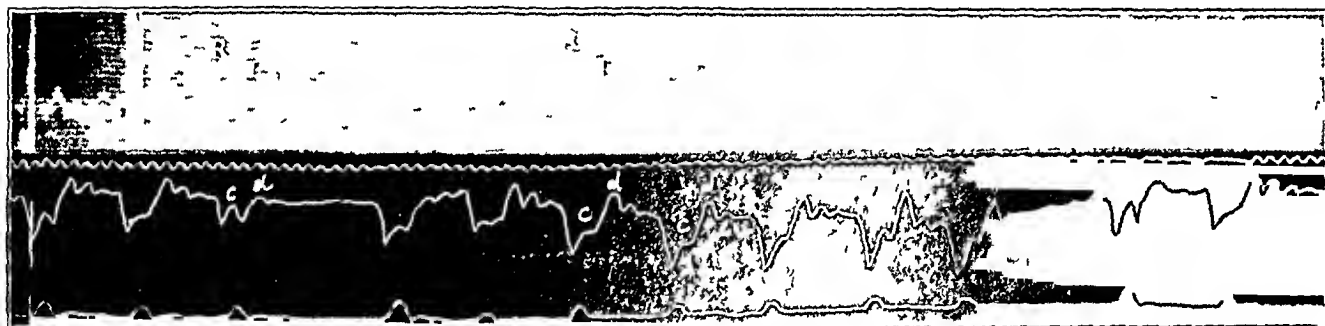


Fig 6 (case 4) —Simultaneous electrocardiogram and epigastrigram and the radial record in auricular fibrillation, showing the defect of the wave a and the peak P, and in some part of the epigastrigram the partially positive wave *s'* which looks like the wave a. This epigastrigram belongs to the form of pulmonary emphysema, according to the classification of figure 1.

SUMMARY

From the five cases mentioned, it can be easily understood that the peaks P, R and T of the electrocardiogram correspond minutely with the waves a, c and d, respectively, of the epigastrigram.

In the first place, from the comparison and analysis of the simultaneous tracings of the epigastrigram with several polygrams it was revealed that the wave a has its origin in the contraction of the right auricle, and this hypothesis that the wave a of the epigastrigram corresponds exactly with the peak P of the electrocardiogram in the former report gains confirmation through the results described here. The following facts are noteworthy. The wave a of the epigastrigram in figure 2, which represents the disturbance of atrioventricular conduction coincides with the peak P of the electrocardiogram and in figure 5 the wave a of the epigastrigram flattens in entire accordance with the flattening of the peak P of the electrocardiogram.

Second, it is evident that the wave c or the peak s' of the epigastriogram is related to the ventricular contraction, because the wave c or the peak s' corresponds entirely with the peak R of the electrocardiogram

Third, though there is much discussion about the nature of the peak T of the electrocardiogram, it is quite interesting that the wave d of the epigastriogram coincides exactly with the peak T

MYCOTIC ANEURYSM OF THE AORTA^{*}

FRED M SMITH, M D

AND

G H HANSMANN, M D

IOWA CITY

Mycotic aneurysms of the aorta occasionally develop during the course of intravascular infection. In most instances they are associated with a subacute bacterial endocarditis. They are usually small and rarely discovered until necropsy. This case is of interest because of the size and location of the aneurysm and the associated pathology.

REPORT OF CASE

History—R F, a boy, aged 17 years, was admitted to the University Hospital, Jan 7, 1925. He complained of distress in the precordial region, pain in the left hip, weakness, and epistaxis. He stated that he had had measles and whooping cough in early childhood and rheumatic fever in 1919. After the latter illness the medical history was negative except for an occasional cold.

The present illness began in October, 1924, with fever, night sweats, loss of weight and frequent nosebleeds. He had had a daily afternoon temperature which usually reached 102 F. In November he was told by his family physician that he had heart trouble. The precordial pain was the chief complaint. It was very severe at times and aggravated by deep breathing. He had experienced, on a few occasions, severe pain in the upper left quadrant of the abdomen which appeared suddenly and in one instance lasted several hours. A few days prior to entering the hospital the left hip became sore and painful. He had lost 15 pounds (68 Kg) in weight and felt weak.

Physical Examination—The patient was slender, pale and poorly nourished. A petechial hemorrhage was discovered in the conjunctiva of the right eye. Others were seen in the axilla and on the abdomen. There was a generalized adenopathy. The glands were firm and varied from pea to hazelnut size. The lungs were negative. A prolonged systolic murmur was heard over the left chest, posteriorly. The cardiac impulse was diffuse and extended slightly outside the midclavicular line in the fifth interspace. A diastolic shock was felt over the entire precordia and there was a suggestive thrill. A systolic murmur was heard at the apex. It was even louder in the axillae and had a whistling quality. This was apparently the same murmur heard over the back. The second sound at the base was markedly accentuated. It was loudest to the right of the sternum and ringing in character. A diastolic murmur was heard in the second left interspace. The pulse was quick, but not distinctly water-hammer in character. The systolic blood pressure was 120 and the diastolic 60 mm of mercury. The spleen was palpated and tender on pressure. The left hip was tender and painful on motion. The temperature, pulse and respiration were 101, 104 and 28, respectively. The red blood cell count was 3,190,000, the white count 9,800, and hemoglobin 46 per cent. In the differential count there were 83 per cent polymorphonuclears, 15 per cent lymphocytes, 1 per cent large mononuclears, and 1 per cent basophils. There was a marked variation in the size and shape of the red blood cells. The urine continually showed albumin, hyaline and granular casts and pus cells. On a few occasions

^{*} From the departments of internal medicine and pathology, State University of Iowa College of Medicine.

red blood cells were seen and the chemical test for hemoglobin was positive *Streptococcus viridans* was isolated from the blood

In the roentgenogram of the chest taken January 7 there was a large spherical shadow which seemed to be continuous with the upper left aspect of the heart (fig 1) In the fluoroscope examination the mass could not be separated from the heart and did not pulsate January 9, a pleural friction rub was discovered to the left of the sternum in the third and fourth intercostal spaces The following morning the friction rub was still present and the percussion note at the base of the left lung was impaired The breathing sounds were distant and bronchial in character During the meantime the pain in the precordium continued, the breathing was more difficult and the coughing had increased A needle was introduced into the left pleural cavity and 250 cc of bloody fluid was withdrawn This fluid contained numerous red blood cells and only an occasional white blood

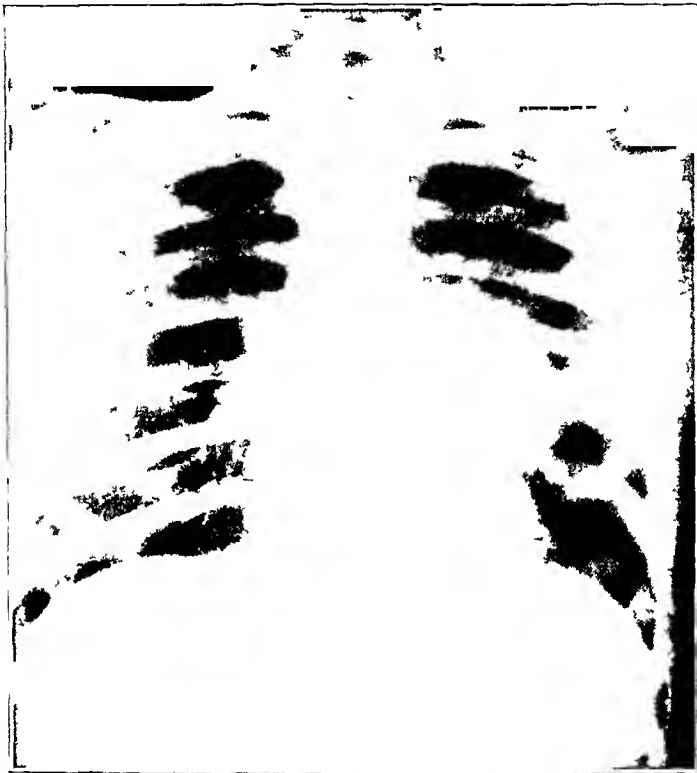


Fig 1—Jan 7, 1925, aneurysm protruding into the left chest cavity

cell Cultures were made which remained sterile During the night of January 16, the patient experienced severe pain in the precordial region which was aggravated by breathing and coughing The signs of fluid in the left side of the chest increased The roentgenogram (fig 2) showed marked density of the entire left side of the chest and the heart and mediastinum seemed to be pushed to the right Hereafter the course was rapidly downward and the patient died suddenly, January 28, following a short paroxysm of coughing During the period of observation the temperature ranged from 98 to 104

Necropsy Findings—The body was poorly nourished and extremely pale Petechial hemorrhages were seen in the conjunctiva, the axillae and on the chest There was a large ecchymosis on the left hip The peritoneal cavity contained 200 cc of straw colored fluid In the right pleural cavity a few fibrous adhesions were found The left chest contained 2,000 cc of recently coagulated blood A

thick coat of fibrinous material was adherent to the left lung. The heart was in the normal position and weighed 370 Gm. The margin of the mitral valve was thickened and there were a few warty vegetations. There were only two aortic cusps and on each were recent fibrous vegetations which extended downward on the wall of the left ventricle. The muscle was pale and flabby. The aorta was mottled by the early lesions of arteriosclerosis. At the site of the opening of the ductus arteriosus during embryonic life, the aorta was constricted to less than half the normal size. A centimeter below this constriction, there was an opening into the wall of the aorta approximately 3 cm in diameter. This opening connected with an aneurysmal sac 6 cm in diameter which projected into the left chest (figs 3 and 4). It was filled with an antemortem clot. The outer wall was composed of pleura and adventitia of the aorta. The remaining structure of the aorta had apparently been destroyed. The aneurysm had ruptured into the left chest cavity. Infarcts were found in the spleen and kidneys. There was a passive congestion of the liver and edema of the ankles.



Fig 2—Jan 17, 1925, marked density of the entire left chest and the mediastinum, the heart is pushed to the right. The effusion was thought to have resulted from the slow leakage of blood into the left chest and mediastinum.

In the histologic examination, the aorta in the vicinity of the aneurysm was normal. At the base of the aneurysm, however, the wall was destroyed except for frayed out elastic fibers, among which streptococci were seen. The greater portion of the wall of the aneurysm was composed chiefly of an antemortem clot supported by fibrous connective tissue. The liver, kidney and heart showed focal areas of necrosis.

COMMENT

The case here reported had the typical clinical manifestations of a subacute bacterial endocarditis in which *Streptococcus viridans* was the responsible organism. Even though the course was rapid the fatal termination was hastened by the rupture of a mycotic aneurysm.

The size and location of the mycotic aneurysm was unusual. In an extensive review of the literature, Stengel and Wolferth¹ were able to compile 213 cases and added four of their own. In sixty-six instances the aorta was involved, and a total of eighty-eight was found. The



Fig 3—Location of the aneurysm and site of the rupture

aneurysms of the aorta were usually small and most frequently involved the root and ascending portion. Grant² has more recently made a careful study of the aortic lesions in thirty cases of subacute bacterial

1 Stengel, A., and Wolferth, C. C. Mycotic (Bacterial) Aneurysms of Intravascular Origin, *Arch Int Med* **31** 527 (April) 1923

2 Grant, R. T. The Aortic Lesions of Subacute Infective Endocarditis, *Heart* **11** 9 (Jan.) 1924

endocarditis in some of which mycotic aneurysms were discovered. In all instances the lesions were found in the root or in the immediate vicinity of this section of the aorta. In one of the cases reported by Reifenstein³ the aneurysm was located in the first portion of the descending aorta and in some respects resembled the present case in



Fig. 4—Opening of the aneurysm into the aorta, constriction of the aorta at the upper level of the aneurysm

that above the aneurysm in each instance there was a constriction of the aorta. In our case there were warty vegetations on the mitral valve which had been previously damaged by a rheumatic infection. More

3 Reifenstein, B. W. Two Cases of Mycotic Aneurysm, Gonococcal and Pneumococcal in Origin, *Am J M Sc* **168** 381 (Sept.) 1924

recently developed and extensive vegetations were seen on the aortic valves. In this connection it is to be recalled that there was a congenital absence of one aortic cusp. It is generally known that subacute bacterial endocarditis is often associated with congenital defects of the heart. In a series of thirty-one cases of subacute bacterial endocarditis studied by Lewis and Grant⁴ 26 per cent had a congenital bicuspid condition of the aortic valves. They concluded that the congenital defect increased the susceptibility to the disease. It is possible that the impediment in the circulation induced by congenital defects is a factor contributing to the localization of the infection at these points. The constriction of the aorta in our case and the defect in the aorta reported by Reifenstein must have produced considerable interference with the flow of the blood. The configuration of the root of the aorta apparently favors the development of infection in this location. The involvement of this portion of the aorta in the absence of vegetations on the aortic cusps supports this conception.

The question of whether the mycotic aneurysm is produced by an infection of the intima or an infected embolus to the media by the vasavasorum is in dispute. The findings in the cases reported by Koritschoner⁵ and Klotz⁶ favor the latter conception. Furthermore, Quinby⁷ and Dafoe⁸ record instances in which mycotic aneurysms followed infection about the aorta. In the latter the aortic wall was invaded by an infection from adjacent tuberculous glands. In the study made by Grant, however, that portion of the aorta in which the intima was normal, the deeper layers, was free from inflammatory changes. He furthermore noted that the lesions in the aorta were very near the vegetations on the aortic valve or within the immediate vicinity. In the present case it is to be recalled that the aorta, up to the aneurysm, was normal. Should the damage have been produced by emboli to the vasavasorum, one would ordinarily expect to find a pathologic condition elsewhere in the media. It would thus seem that the evidence so far favors the intimal origin of mycotic aneurysm in the majority of instances.

Even though the pathologic findings in mycotic aneurysms are similar, a great variety of organisms have been identified in those

4 Lewis, T, and Grant, R. T. Observations Relating to Subacute Infective Endocarditis, *Heart* **10** 21 (April) 1923.

5 Koritschoner, R. Beitrag zur Kenntnis der mykotischen Aortitis, *Centralbl f allg Pathol u path Anat* **23** 100, 1912.

6 Klotz, O. Arterial Lesions Associated with Rheumatic Fever, *J Pathol & Bacteriol* **18** 259, 1913.

7 Quinby, W. C. Report of a Case of Infectious Aneurysm of the Aorta, *Boston M & S J* **184** 14, 1921.

8 Dafoe, W. A. Ruptured Aneurysm of Abdominal Aorta Due to Tuberculosis, *Edinburgh M J* **32** 291 (June) 1925.

instances in which the infectious agent was investigated. It is thus evident that the type of organism plays a minor rôle in the production of the mycotic aneurysm. In the present case *Streptococcus viridans* was responsible for the vascular injury. This organism is considered to be the least virulent of the streptococcus group and is thought by some to be incapable of producing a lesion unless there is a preexisting injury that favors its localization. In our case, however, there was an extensive destruction of the aortic wall and the aneurysm was as large as any heretofore reported. It would therefore seem that the cultural characteristic of the streptococcus on artificial mediums does not necessarily enable one to predict the type of lesion that they will produce in the living organism. The fact is not infrequently observed during postmortem examination and suggests that desirability of more precise biologic methods of studying the pathogenic organism.

In the present case the size and location of the aneurysm were such that it was possible to make a diagnosis before death. This type of aneurysm, however, is seldom recognized during life because of the small size and the frequent location in the root of the aorta. No doubt more would be diagnosed if the possibility was considered in every case of subacute bacterial endocarditis. They are apt to rupture and this feature should suggest the diagnosis. In our case the extensive deposit of fibrin on the lung and the infiltration of the mediastinum indicated that there was probably a slight amount of blood escaping from the aneurysm for several days before the fatal hemorrhage.

THE PHARMACOLOGY AND THERAPEUTICS OF NOVASUROL¹

A M SERBY, M D

CHICAGO

Novasurol, mercuricoxyacetobarbital, contains 33.9 per cent of mercury and is prepared in a 10 per cent aqueous solution. It was introduced in 1917 as an antisymphilitic. Voigt¹ and Levy-Lenz² in 1920 summarized its effect in syphilis. Compounds of mercury, principally calomel, have always ranked high among the diuretics. Increase in urination was early noted with novasurol, and in 1920 attention was called to this effect by Saxl and Heilig³. They found marked polyuria and a quantitative increase in the excretion of sodium chloride, both of which could be stopped by the use of atropine. They believed the effect was secondary to hydremia.

Brunn⁴ in 1921 gave normal persons 1 or 2 liters of salt water before injection of novasurol, and obtained the same results as in cases of syphilitic myocarditis with decompensation, namely, great augmentation of the urinary total. At necropsy of the syphilitic cases, he noted no renal lesions.

Nonnenbruch⁵ in 1922 agreed with Saxl and Heilig that the action was extra-renal and due to the mobilizing of sodium chloride and water from the tissue spaces into the blood, with a secondary overflowing of these substances from the blood into the urine, and therefore to no selective action on the kidneys.

Bleyer⁶ in 1922 thought the hydremia theory plausible, but was not satisfied with the proofs available. Bohn⁷ in 1923 concluded novasurol worked extrarenally. Tezner⁸ in 1923 obtained a more rapid absorption

¹ From the department of medicine and the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

¹ Voigt. Novasurol, Therap. Halbmonatsh. **34** 263 (May 1) 1920.

² Levy-Lenz. Erfahrungen mit Novasurol, Therap. Halbmonatsh. **34** 388 (July 15) 1920.

³ Saxl, P., and Heilig, R. Ueber die diuretische Wirkung von Novasurol- und anderen Quecksilberinjektionen, Wien klin. Wchnschr. **33** 943 (Oct 21) 1920.

⁴ Brunn, F. Zur Wirkung des Novasurols als Diuretikum, München med. Wchnschr. **68** 1554 (Dec 2) 1921.

⁵ Nonnenbruch, W. Ueber die Wirkung des Novasurols auf Blut und Diurese, München med. Wchnschr. **68** 1282 (Oct 7) 1921.

⁶ Bleyer, L. Erfahrungen über die Novasurol-diurese, Klin. Wchnschr. **1** 1940 (Sept 23) 1922.

⁷ Bohn, H. Experimentelle Studien über die diuretische Wirkung des Novasurols, Klin. Wchnschr. **2** 352 (Feb 19) 1923.

⁸ Tezner, O. Zum Mechanismus der Novasurolwirkung, Med. Klin. **19** 788 (June 10) 1923.

of subcutaneously injected physiologic sodium chloride solution in children following novasurol, and therefore declared the mechanism outside the kidney. Fodor⁹ in 1923 claimed that because atropine stops the diuresis of novasurol the chemical affects a brain center which controls the metabolism of water and sodium chloride. Schlayer¹⁰ in 1922 and Schur¹¹ in 1923 maintained a direct renal hypothesis. Crawford and McIntosh¹² in 1925 combined several ideas as follows: (a) For the first three hours hydremia exists, (b) following that a concentration of the blood occurs, and (c) this, with direct renal stimulation, causes the later increased flow.

Many observers obtained diuresis in cardiac edema by giving novasurol either intramuscularly or intravenously every three or four days. In markedly decompensated persons, however, its action has been best induced when injected intravenously with strophanthin. The diuresis usually appears within two hours and extends over twelve hours during which time the quantity may reach 2 or 3 liters. Bohn¹³ in 1924, however, found that this increased urination may last twenty-four hours. As high as 2 or 3 pounds (0.9 or 1.4 Kg.) in weight may be lost in one day, and during prolonged administration as much as 20 or 30 pounds (9 or 13.6 Kg.). Clinically, great improvement and a gradual resumption of compensation in cardiac cases has accompanied the polyuria. The dyspnea, cyanosis, râles, edema and fluid in the abdomen, chest and extremities have cleared up.

Edema due to syphilitic, rheumatic or sclerotic heart valvular and muscular injury has been benefited. Novasurol has been resorted to only when digitalis, rest in bed and dietary measures have proved unsuccessful. In some cases with tense abdominal walls due to ascites paracentesis was first necessary. The action has been best marked in cases of decompensation accompanied by high blood pressure and cyanosis. Inflammatory exudates, intrapleural and intraperitoneal, tuberculous and nontuberculous, ascites due to cirrhosis of the liver or carcinomatosis of the peritoneum may be alleviated but not cured. In renal edema, novasurol is a distinct menace and will increase kidney damage. In diabetes mellitus, Bohn¹³ found a lowering of the blood sugar and a disappearance of the glycosuria. In syphilis, its use with arsphenamine as a mercurial has been accepted by many authorities.

⁹ Fodor, E. Ueber das Indikationsgebiet des Novasurols als Diuretikum, *Med Klin* **19** 684 (May 20) 1923.

¹⁰ Schlayer. Stauungsniere, essentielle Nierenschädigung und Novasurolanwendung, *Med Klin* **18** 1425 (Nov 5) 1922.

¹¹ Schur, H. Klinisch-experimentelle Studien über Novasurol-diurese und Nierenfunktion, *Wien Arch f inn Med* **6** 175, 1923.

¹² Crawford, J. H., and McIntosh, J. F. Use of Novasurol in Cardiac Edema, *J Clin Investigation* **1** 333 (April) 1925.

¹³ Bohn, H. Fortgesetzte Studien über Novasurol, *Deutsches Arch f klin Med* **143** 225 (Dec) 1923.

TABLE 1—Changes Following Novasurol

Date	Blood						Urine				Fluid	
	Novasurol, Cc	Non-protein Nitrogen	Urea Nitrogen	Sugar	Bilirubin		Albumin	Casts	7 a m to 7 p m	7 p m to 7 a m	In take	Output
					Direct	Indirect						
Case 1 Mitral Insufficiency												
10/19/24							+++	Many				
10/20/24							++	Many			810	
10/21/24*	0.5						++				1,650	1,080
10/22/24							+				1,070	1,140
10/23/24	0.5						+				1,230	810
10/24/24											1,050	960
10/25/24	1.0						++				1,091	3,780
10/26/24							Trace	Few			1,470	1,380
10/27/24	1.0						Trace				1,530	2,280
10/28/24							Trace				1,410	1,920
10/29/24	1.0						Trace				830	2,400
10/30/24							Trace				1,230	1,020
10/31/24*	1.0						Ft tr				1,290	2,220
11/ 1/24											1,500	1,260
11/ 2/24	1.0						Ft tr	Few			1,170	2,220
11/ 3/24							Trace				1,500	1,620
11/ 4/24	1.0										930	2,220
11/ 5/24							+	Occas			1,500	960
11/ 6/24	1.0										990	2,220
11/ 7/24							Trace				1,344	1,320
11/ 8/24	1.0										1,155	3,360
11/ 9/24											1,184	1,200
11/10/24	1.0						Trace				1,376	2,700
11/11/24*											1,500	1,380
11/12/24	1.0										1,536	1,440
11/13/24							Trace	Occas			1,184	1,200
11/14/24	1.0						Trace				1,500	1,680
11/15/24							Ft tr				1,352	1,200
11/16/24	1.0						Trace				1,376	2,400
11/17/24							Trace				1,248	1,680
11/18/24	1.0						Trace	Occas			1,500	1,980
11/19/24											896	1,320
11/20/24	1.0										1,500	1,440
11/21/24*							+				1,000	660
11/22/24	1.0										1,216	1,260
11/23/24											896	960
11/24/24	1.0										1,450	780
11/25/24							++	Occas			1,500	600
11/26/24											1,504	1,260
Case 2 Aortic and Mitral Insufficiency												
12/23/24							+	0	246	286	1,500	532
12/24/24	1.0	44	28	89	+	+	Trace	0	470	552	1,020	1,022
12/25/24							+	0	190	845	1,800	1,035
12/26/24							++	Many	540	376	1,590	916
12/27/24	1.0						+	0	551	205	1,580	756
12/28/24							+	0	414	196	1,680	610
12/29/24	1.0						Trace	0	1,555	174	1,500	1,729
12/30/24							Trace	0	245	250	1,050	495
12/31/24		55		95	+	+	Trace	0	347	230	1,080	577
1/ 1/25	1.0						Trace	0	2,215	1,165	1,350	3,380
1/ 2/25							Trace	0	222	170	2,140	392
1/ 3/25							Trace	0	258	302	1,140	560
1/ 4/25	1.0						Trace	0	960	475	1,020	1,435
1/ 5/25							Trace	0	460	280	840	740
1/ 6/25							Trace	0	292	412	1,080	701
1/ 7/25	1.0	60	32	58	+	++	0	0	935	742	720	1,677
1/ 8/25							0	0	407	356	900	763
1/ 9/20							0	0	368	418	1,140	786
1/10/25	1.0						0	0	1,762	747	960	2,509
1/11/25							0	0	597	368	900	965
1/12/25							0	0	594	515	840	1,009
1/13/25	1.0						0	Few	1,527	649	1,260	2,176
1/14/26							Trace	Few	395	720	1,110	1,115
1/15/25		58	30		+	++	Trace	Many	242	487	900	729
1/16/25	1.0						Trace	Many	1,453	555	1,170	2,008
1/17/25							Trace	0	1,100	605	1,200	1,705
1/18/25							+	0	313	174	1,080	487
1/19/25		63			Trace	Neg	Trace	0	562	746	1,410	1,308
Case 3 Cardiosclerosis and Arteriosclerosis †												
12/ 2/24							Ft tr	0				400
12/ 3/24	0.5	48	24		0	++++	Ft tr	0			870	600
12/ 4/24		40	20		Trace	++++	Ft tr	0			1,260	180
12/ 5/24	1.0							0			960	1,020
12/ 6/24							Ft tr	0			1,312	1,120

* Weight 10/21/24 190 pounds (86.2 Kg.) 10/31/24, 173 pounds (78.5 Kg.) 11/11/24, 155 1/2 pounds (70.5 Kg.), 11/21/24, 151 1/2 pounds (68.7 Kg.)
† Large share of output in fluid feces

TABLE 1—Changes Following Novasurol—(Continued)

Date	Blood						Urine				Fluid	
	Nova- suroi, Cc	Non protein Nitrogen	Urea Nitro gen	Bilirubin		Albu min	Casts	7 a m to 7 p m	7 p m to 7 a m	In take	Out- put	
				Sugar	Direct Indirect							
12/ 7/24	1 0						0			1,106	1 580	
12/ 8/24						Ft tr	0	443	180	912	621	
12/ 9/24						Ft tr	0	125	188	1,020	313	
12/10/24	1 0	42	26		Trace + + + +	Ft tr	0	690	505	970	1,105	
12/11/24						Ft tr	0	305	285	1,020	590	
12/12/24						0	0	310	150	1,184	760	
12/13/24	1 0					0	0	520	524	1,020	1,150	
12/14/24						Trace	0	410	220	916	630	
12/15/24						0	0	180	162	864	312	
12/16/24	1 0	41	22		Trace +	0	0	330	270	780	600	
12/17/24						0	0	130	230		360	
Case 4 Diabetes Mellitus and Cardiosclerosis												
12/22/24		35	15	196	0	0	0	930	525	1,446	1,455	
12/23/24							0	830	1,140	1,290	1,970	
12/24/24	1 0						Trace	0	1,470	958	1,380	
12/25/24							Trace	0	798	1,438	1,500	
12/26/24							Ft tr	0	1,510	1,306	1,260	
12/27/24	1 0						Ft tr	0	1,469	600	780	
12/28/24							Ft tr	0	1362?		230	
12/29/24		37	15	266 276 258 238 204 185			0	0	1,194	615		
12/30/24	1 0				0	Trace	+	0	1,245	680	1,925	
Case 5 Aortic Stenosis												
1/ 8/25							0	0		80	900	
1/ 9/25		50	25	95	+	+	0	0	41	153	140	
1/10/25							0	0	88	158	2,700	
1/11/25							0	0	201	114	0	
1/12/25	0 5						Trace	Many	233	84	900	
1/13/25							Trace	Many	?	0	?	
1/14/25								Many	?		90	
1/15/25	0 5							Many		503	270	
1/16/25	Patient died suddenly											
Case 6 Hypertension and Chronic Nephritis												
3/15/25							++				2,130	
3/16/25							++				1 890	
3/17/25	0 2	100		111			+	Many			1 800	
3/18/25							+				1 800	
3/19/25							+				1 890	
3/20/25	0 4						+				1 800	
3/21/25							+				1 815	
3/22/25							+				1 800	
3/23/25	0 6	50		91			Trace				1 815	
3/24/25							+				1 820	
3/25/25							+				1 800	
3/26/25	0 8						+				1 860	
3/27/25							++	Few			1 800	
3/28/25							++	Few			1 830	
3/29/25	1 0						+	Many			1 980	
3/30/25							+	Many			1 950	
3/31/25							+					
4/ 3/25	Died in uremia											

The ill effects of novasurol are few but generally agreed on, namely, gingivitis, hemorrhagic benign colitis, and occasionally renal damage. Saline cathartics should not be administered with novasurol.

METHOD OF INVESTIGATION

Six cases of marked cardiac decompensation were studied. Salt was restricted to 2 or 3 Gm daily. Fluid intake was limited and measured. The patients were given treatment of rest in bed, digitalization and

restriction of fluids and salt before novasurol was begun. In some cases digitalis was continued with the novasurol. Fluid output, in urine and feces, was estimated in twelve hour periods. Albumin determinations and microscopic examinations were made of each specimen of urine. Each week, blood chemical studies, including nonprotein nitrogen, urea nitrogen, sugar, plasma proteins, both albumin and globulin, and van den Bergh bilirubin were made.

The novasurol¹⁴ was injected before breakfast at 7 a. m. The interval in the early work was two days but later three or four days. The dosage was small, in case 6 only 3 minims at first, gradually increased to 1 cc. The route of introduction was at first intramuscular, but later intravenous.

REPORT OF CASES

CASE 1—J. L., a bartender, aged 51, had mitral insufficiency. On admission, his complaints were as follows: ascites, four weeks; swelling of feet, two weeks; dyspnea, tightness across the chest and decrease in urinary output for three days. His face was puffy and pasty. The left heart border extended to the anterior axillary line, the right heart border to outside the right sternal border. The heart tones were faint and indistinct. There were some dulness and suppressed breath sounds at the right base posteriorly and a few coarse râles at both bases. The abdominal wall and sacral regions pitted on pressure. The abdomen was tense, distended, dome shaped and dull to percussion. The liver edge, tender and

TABLE 2—*Effects of Novasurol on Plasma Proteins in Case 2*

	Plasma Protein, per Cent	Albumin, per Cent	Globulin, per Cent	Ratio	
				Albumin	Globulin
Before novasurol					
1/14/25, 7 00 a. m.	7.39	4.43	2.96	60	40
After novasurol					
1/14/25, 7 30 a. m.	6.55	4.26	2.29	65	35
9 00 a. m.	7.21	4.54	2.67	63	37
11 00 a. m.	6.82	4.64	2.08	68	32
1 00 p. m.	6.61	4.56	2.05	69	31
3 00 p. m.	6.86	5.28	1.58	77	23
5 00 p. m.	6.52	5.41	1.11	83	17
7 00 p. m.	7.57	4.69	2.88	62	38
1/15/25, 7 00 a. m.	9.05	8.15	0.90	90	10

smooth, could be palpated and percussed 6 cm. below the costal margin. His lower extremities were edematous almost up to the knees. The history was suggestive of syphilis, but the blood Wassermann reaction was negative. Under routine treatment, the urinary output reached 800 cc. daily, the stools were frequent and fluid. The anasarca decreased slightly, but persisted in the abdomen and ankles. Novasurol was tried intramuscularly, 0.5 cc. and later 1 cc. every other day. An abdominal paracentesis removed 1,200 cc. of clear ascitic fluid. The fluid output at once rose from 800 to 2,400 cc. daily, at first largely in the stools, but later only in the urine. Simultaneously the weight dropped from 190 to 153 pounds (86.2 to 69.4 Kg.), the dulness and distention of the abdomen, the fluid and râles at the bases, and the edema of the ankles disappeared.

CASE 2—M. S., a salesman, aged 40, had rheumatic pancarditis, aortic and mitral insufficiency and auricular fibrillation. He complained of edema of the feet for six weeks, vertigo for three weeks, and insomnia for six days. He was

¹⁴ The novasurol used in this study was supplied by the Winthrop Chemical Company.

markedly cyanosed and dyspneic. The thyroid was slightly and diffusely enlarged. The left heart border reached the posterior axillary line, the right heart border the right sternal border. At the apex one heard a loud systolic, followed by a middiastolic murmur. The right posterior base was dull and presented many coarse moist râles. The liver edge was tender four fingers below the costal margin. Both flanks showed shifting dullness and the feet pitted on pressure. The blood pressure was 130 systolic, 75 diastolic. Digitalization did not remove the anasarca. Five hundred cubic centimeters of fluid was removed from the right chest and novasurol therapy begun intramuscularly, but no benefit followed. The novasurol was then administered intravenously and in one month the edema of the feet, the ascites and râles, the cyanosis and dyspnea had disappeared.

CASE 3—J. C., a tailor, aged 62, had cardiosclerosis and arteriosclerosis. He complained of chest pain and dyspnea for four years, and swelling of the feet for four weeks. His color was subicteric. The heart borders were enlarged to the right and left, and the heart tones were faint. Over the right posterior base one noted flatness and diminished breath sounds. The liver edge was smooth and tender five fingers below the costal margin. Examination revealed edema up to the mid thigh bilaterally and over the sacrum and slight dullness in the flanks. The blood pressure was 150 systolic, 94 diastolic. Under rest and digitalis he improved slightly. Novasurol, intravenously, caused diuresis and cleared up the cyanosis, dyspnea and retention of fluid.

TABLE 3—Effect of Novasurol on Blood Sugar and Glycosuria in Case 4

	12/29/24	12/30/24	Remarks
8 00 a. m.	266 mg per 100 cc	238 mg per 100 cc	1 cc of novasurol given at 8 05 a. m., 12/30/24
9 00 a. m.	276 mg per 100 cc	204 mg per 100 cc	
10 00 a. m.	258 mg per 100 cc	163 mg per 100 cc	
Glycosuria	9.0 Gm	7.5 Gm	

CASE 4—B. Z., a man, aged 58, had diabetes mellitus, cardiosclerosis and arteriosclerosis. He complained of polyuria, polydipsia and polyphagia for five weeks, dyspnea, weakness, and edema of the feet for two weeks. His skin was dry and the body was emaciated. There was a slight diminution of breath sounds over the bases. The heart borders were within normal limits, the radial arteries were hard and tortuous. The liver could not be palpated. Slight puffiness was noted over the feet. On the entrance day he excreted 63 Gm of glucose. Under a rigid diet and digitalis the edema did not disappear. After one injection of novasurol, good diuresis occurred, the blood sugar fell and the swelling of the feet disappeared.

CASE 5—S. Z., a shoemaker, aged 52, had aortic stenosis, mitral stenosis and insufficiency. He complained of dyspnea, cough and swelling of the abdomen and lower extremities for one week. There was moderate cyanosis and dyspnea. Numerous moist râles were present over both bases. Cardiac examination showed both heart borders to be outside the normal limits and a rough systolic thrill and murmur over the aortic area transmitted to the neck. The pulses were rapid and irregular. The liver edge was 11 cm below the costal margin. The blood pressure was 120 systolic, 85 diastolic. Usual treatment did not improve the condition. An intravenous small dose of novasurol did not produce increased urination and the edema became worse. Sudden death occurred four days later.

CASE 6—O. S., a salesman, aged 35, had hereditary hypertension and chronic nephritis. He entered the hospital because of cough, dyspnea, nocturia, progressive swelling of the lower extremities and apparent gain in weight. A slight exophthalmos was noted. Both lung bases were dull on percussion. The heart was enlarged to the right and left and a slight systolic murmur was heard at the base. The liver edge was tender and extended a hand's breadth below the costal margin. There was shifting dullness in the abdomen, edema over the

sacrum and extending up both lower extremities to mid thigh. The anasarca decreased slightly under usual care until an attack of follicular tonsillitis with high fever occurred, accompanied by suppressed urination and a return of the fluid retention. Intravenous novasurol in small increasing doses caused excellent diuresis. The edema lessened again, but the stupor deepened gradually and the patient died.

RESULTS

I *Changes in Body Weight*—Clinical improvement and diuresis were always accompanied by loss in weight. In case 1, this amounted to 35 pounds (15.9 Kg) in three weeks. In the other cases, the patients' conditions precluded keeping a definite record. Concomitant with the weight decrease, the patients became very thin, since the decompensation had caused not only edema but also real tissue damage. Simultaneously, the dyspnea, râles, hydrothorax, ascites and edema of the extremities, both of subcutaneous tissues and musculature, vanished. In some instances, the size of a leg decreased one-third in diameter.

II *Blood Changes*—(a) Nitrogenous Elements. In case 2, the nonprotein nitrogen and urea nitrogen rose from 44 and 28 mg per hundred cubic centimeters, respectively, to 63 and 30 mg in twenty-four days. In case 3, in thirteen days the nonprotein and urea nitrogen fell from 48 and 24 mg per hundred cubic centimeters to 41 and 22 mg. In case 4, the nonprotein and urea nitrogen were practically unchanged at the end of a week. Patient 5 with signs of marked cardiac decompensation and nonprotein and urea nitrogen of 50 and 25 mg per hundred cubic centimeters died at the end of one week. Case 6, with nonprotein nitrogen of 100 mg per hundred cubic centimeters, presented a drop to 50 mg per hundred cubic centimeters under cautious treatment, but coma deepened and the patient died.

The clinical results agree sufficiently with the forecast of the nitrogenous constituents of the blood to lead us to believe the latter are of some value. As Crawford and McIntosh¹² have asserted, novasurol may act chiefly through renal stimulation. Since it is a mercurial compound, it may cause renal damage, if not as novasurol, then in some other form of mercury produced in the metabolic processes. From the data obtained, we think novasurol is a renal irritant. It should be begun in low dosage and with great caution if nitrogenous retention is evident, and should not be administered over long periods.

(b) Sugar. The blood sugar was not pathologically altered during use of novasurol. In case 2, the level was 89 mg per hundred cubic centimeters at the beginning and 58 mg at the end of fourteen days. In case 6, in seven days the blood glucose fell from 111 mg per hundred cubic centimeters to 91 mg. Bohn¹³ found that the hyperglycemia of diabetes is reduced by novasurol. To corroborate this we studied case 4, one of diabetes mellitus, arteriosclerosis and moderate edema. We stopped insulin and allowed a full diet without sugar. In table 3, we

show the blood sugar at 8 a m, 9 a m and 10 a m, namely, 266 276 and 258 mg per hundred cubic centimeters, respectively. On the next day at 8 a m the blood sugar was 238 mg. Five minutes later 1 cc of novasurol was given and at 9 a m the blood glucose was 204 and at 10 a m 185 mg. The first day 9 Gm and the second day 7.5 Gm of sugar were excreted. The explanation of the discrepancy between blood sugar and urinary sugar is not easy. However, it seems to corroborate the early hydremia postulated by Crawford and McIntosh. The lowering of the blood sugar is more apparent than actual, as proved by the glycosuria of 9 Gm the first day and 7.5 Gm the second day. Novasurol probably does not aid in the utilization of available sugar.

(c) Bilirubin. As a further check on the toxicity of novasurol we made determinations of bilirubin by the van den Bergh method. We have followed the interpretations of McNee.¹⁵ In case 2 both the direct and indirect were positive at the beginning of treatment denoting a damaged liver, here probably due to decompensation. During the prolonged administration of novasurol the direct remained about the same, but the indirect became stronger, thus probably pointing to increased liver damage, this time due to the medication itself. This agrees with the fact that novasurol injures the kidney and raises the blood nitrogenous substances. Within three days after the disappearance of the edema and the cessation of novasurol, the direct became a trace and the indirect negative. In case 3, in which novasurol was prescribed for only fourteen days and the nonprotein nitrogen was low, both the direct and the indirect bilirubin decreased. In case 4, bilirubin study demonstrated novasurol as innocuous over a short period, corresponding in this respect with the results obtained from blood nitrogen determinations. In case 5, a positive direct and indirect bilirubin and high blood nitrogen estimation gave a poor prognosis. We conclude that novasurol in small quantities for short periods may aid the excretion of bilirubin in chronic passive congestion of the liver. However, in prolonged administration, novasurol may be toxic to the liver.

(d) Plasma Proteins. In table 2 are given the results of novasurol on plasma proteins and blood dilution in case 2. Normally, according to Naegeli,¹⁶ plasma proteins comprise from 6 to 8 per cent of the blood by volume. Of this, about 60 per cent is serum albumin and 40 per cent serum globulin. Our results were obtained by the Pulfrich dipping refractometer and the Hess viscosimeter. The plasma proteins fell for the first six hours, a rise to normal in twelve hours followed, and a concentration much beyond the original point succeeded at twenty-four

¹⁵ McNee, J. W. Jaundice, a Review of Recent Work, *Quart. J. Med.* **16** 390 (July) 1923.

¹⁶ Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, Leipzig, Veit & Co., 1924.

hours The serum albumin, however, did not fall much, and at twenty-four hours its percentage was almost twice that before injection However, the serum globulin dropped irregularly until at twenty-four hours its volume was only 0.9 per cent

We have been led to the following explanation for this At first, an actual dilution and increase of blood volume exists In compensation, reserve tissue albumin passes into the blood to restore the normal viscosity and composition of the blood If, as is claimed by some, albumin constitutes the embryonic and globulin, the mature blood proteins, albumin would be the reserve in such an emergency At twelve hours fluid excretion practically balances blood dilution Hence, although the total blood volume probably surpasses normal, the blood proteins are of normal percentage After twenty-four hours, fluid excretion has further concentrated the blood and left the total blood proteins high and their relation to each other altered

III *Changes in Urine*—(a) Volume Urinary changes are most easily grasped by both clinician and patient In case 1, an initial injection of 1 cc caused a twenty-four hour urinary output of 3,780 cc Each subsequent dose gave rise to an excretion of 2 or 3 liters until the edema disappeared In case 2, intramuscular administrations were followed by only slight diuresis and slight decrease in anasarca Therefore, 1 cc intravenously was used, this led to an output of 3,380 cc of urine This result was attained in case 2 thereafter by the intravenous route In the intervals, a normal excretion of from 600 to 1,000 cc prevailed In case 3, 1,500 cc, only a slight rise, was poured out, but with a clearing of the edema In case 4, the twenty-four hour excretion after each injection was more than 2 liters and the increased flow lasted several days In case 5, one of acute and severe decompensation, no increase in volume was noted In case 6, we note a peculiar circumstance Because of the uremia present when novasurol therapy was instituted, the dosage was first set very low, 0.2 cc, and gradually raised The urinary output responded quickly and reached over 2 liters, where it persisted even on days between injection The anasarca gradually lessened but the uremia simultaneously deepened and caused an abandonment of the treatment This unusual combination of decreasing edema and ascending uremia doubtlessly can be attributed to the diuretic and toxic properties of novasurol

The time and route of excretion of fluid is worthy of notice In cases 2 and 4 the largest amount occurred in the first twelve hours In case 3, the output was distributed over twenty-four hours, and in case 6 over several days Our findings agree with those of Bohn¹³ that the excretion is prolonged over twenty-four hours or more in weakened and senile persons

The urine did not account for the total fluid loss in all cases. A large portion diluted the stools in the early administrations in several cases, such as cases 1 and 6. For this reason, warning against the use of novasurol in hemorrhagic colitis or the ingestion of magnesium sulphate simultaneously with novasurol injection has been sounded. Colonic changes serious enough to cause a cessation of therapy did not occur in this series.

(b) *Albumin and Casts* In each case, urinary albumin and casts were determined daily. In case 1, the urine contained much albumin and many casts. During treatment, the albumin lessened to a trace and the casts to only a few. In case 2, a marked albuminuria cleared with compensation. However, later, as the blood nitrogen rose, albumin appeared. The casts followed a similar course. In case 3, albumin and casts were practically absent throughout. In case 4, no albumin was noted until after a week of treatment. In case 5, also albumin and casts were found only after several treatments. In case 6, albumin and casts were numerous throughout the therapy. Thus, although the albuminuria and casts corresponded usually with other indexes, it is more accurate to judge the effects and toxicity of novasurol by the blood nitrogen, urinary output and clinical course.

COMMENT

Obviously, such a compound should be added to one's armamentarium to be invoked only with great caution. Apparently, all cases of cardiac decompensation except those complicated with severe renal infection or damage may be benefited by the judicious administration of this substance, intravenously or intramuscularly, 1 cc twice weekly. Such therapy will bring out the optimum results, namely, a great outpouring of fluid for twelve, twenty-four or even forty-eight hours. The three or four day interval allows the kidney opportunity to recuperate from the stimulus of the medication. No other diuretic accomplishes as much in cardiac decompensation. However, because of its toxicity, novasurol should not be used until the usual measures, such as rest in bed, digitalis and restricted fluids, have been exhausted. We have proof that, if not properly controlled, it is injurious both to the kidney and liver. The blood nitrogen figures and bilirubin have both mounted with increasing toxemia, uremia and lessened output. Albumin and casts do not guide reliably in this instance because of the chronic passive congestion of the kidneys present.

We agree with Crawford and McIntosh¹² on the pharmacology of novasurol. The drug produces for the first few hours a dilution, and later a concentration, of the blood that reaches its peak in twenty-four hours. We make no attempt to determine why the original hydre-

occurs, nor can we draw any definite conclusions from the authors cited. The increase in blood volume causes the early diuresis. Later, the drug stimulates the kidney to produce the urinary increase. Again we have no definite proof, but the blood nitrogen changes point to a renal action. We agree with Bohn¹³ that the hyperglycemia of diabetes may be reduced by novasurol, but we believe this to be due to hydremia and not to any shift in the availability of the blood sugar as with insulin.

SUMMARY

One cubic centimeter of novasurol intramuscularly or intravenously twice weekly in persistent cardiac edema will cause profuse diuresis.

The appearance of toxicity may be noted by bilirubin determinations.

Novasurol may cause renal damage and should not be used in the face of nitrogen retention and lessened urinary output.

Diuresis appears three hours after administration, it lasts twelve hours in young individuals, and twenty-four or forty-eight hours in elderly and weak individuals.

Novasurol may induce a decrease in anasarca and an increase in uremia simultaneously.

In some cases, novasurol may not cause diuresis, although not producing any renal damage.

THE BASAL METABOLIC RATE IN CASES OF CHRONIC CARDIAC DISEASE AND IN CASES OF HYPERTENSION

SHEPARD SHAPIRO, M D
NEW YORK

In 1916 Peabody, Meyer and DuBois¹ found that patients with compensated cardiac disease showed no increase in basal metabolism. Nine out of twelve cases with dyspnea showed elevations in heat production above normal. They used both direct and indirect calorimetry. The respiratory quotients were between 0.73 and 0.94. They considered the earlier work of others of questionable accuracy because the respiratory quotients were too low.

Peabody, Wentworth and Barker² in 1917 studied twenty-four cases of cardiac disease and used as an additional index the vital capacity. Their results indicated that the rise in heat production was related to the degree of cardiac insufficiency. In direct accord with these observations Aub and DuBois³ reported the respiratory exchange to be increased in cases of hypertension with dyspnea.

The subsequent studies of Peabody, Wearn and Tompkins⁴ on "irritable heart" in soldiers, and of Boothby and Sandiford⁵ on a large series of various types of cardiac disease confirmed the view that cardiac disease per se does not alter the basal metabolism but that other factors, such as dyspnea, are responsible for the elevations in heat production.

Within the last two years several additional reports have appeared in the literature on the influence of certain cardiac disturbances on the basal metabolism. Dieuaide⁶ described a case of paroxysmal tachycardia which showed an increase of 16.7 per cent during a paroxysm in which the patient was dyspneic. The basal metabolic rate was normal during

¹ From the Division of Laboratories, Montefiore Hospital.

1 Peabody, F. W., Meyer, A. L., and Du Bois, E. F. The Basal Metabolism of Patients with Cardiac and Renal Disease, *Arch Int Med* **17** 980 (June) 1916.

2 Peabody, F. W., Wentworth, J. A., and Barker, B. I. The Basal Metabolism and the Minute-Volume of the Respiration of Patients with Cardiac Disease, *Arch Int Med* **20** 468 (Sept) 1917.

3 Aub, J. C., and Du Bois, E. F. The Respiratory Metabolism in Nephritis, *Arch Int Med* **19** 865 (May) 1917.

4 Peabody, F. W., Wearn, J. T. and Tompkins, E. H. The Basal Metabolism in Cases of "Irritable Heart of Soldiers," *M Clin N Amer* **2** 507 (Sept) 1918.

5 Boothby, W. M., and Sandiford, I. Summary of the Basal Metabolism Data on 8,614 Subjects with Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate, *J Biol Chem* **54** 783 (Dec) 1922.

6 Dieuaide, F. R. Observations on the Respiratory Gases in Ventricular Paroxysmal Tachycardia, *Bull Johns Hopkins Hosp* **35** 229 (Aug) 1924.

the interval between attacks. The author believed the added work of the heart and respiratory organs was responsible for the augmented metabolism. He used the Tissot method.

Hamburger and Lev,⁷ using the Benedict apparatus, made sixty-six metabolic rate determinations on seventeen patients with various types of cardiac disturbances. They found that during cardiac decompensation the basal metabolic rate varied from 11.8 to 112.7 per cent above normal. Fever and acidosis were not important influences. While they state that the increased muscular activity resulting from accelerated breathing and cardiac contractions may be responsible for the elevated metabolism they believe that the actual causes of increased basal metabolic rate in decompensated cases of organic heart disease are not known. In a second article⁸ they assert that 75 per cent of the decompensated cases of organic cardiac disease show an increased basal metabolic rate of an average of 39 per cent above normal and that the metabolic rate approaches normal as compensation returns. They report a case of paroxysmal tachycardia in which they found the basal metabolic rate to be elevated 11.1 per cent during the paroxysm. At the same time there occurred tachypnea, which phenomenon alone in a normal person caused a rise of 17.5 per cent in the basal metabolic rate. In addition to the accepted causes for the increased heat production in cardiac decompensation, namely, overactivity of both respiratory and heart muscles, they express the belief that other factors may be responsible for the increased heat production in these cases. They suggest variations of thyroid function as one of these factors, and discuss the possibility of a "transient hyperthyroidism during decompensation or changes in the thyroid circulation from long standing congestion of the superior circulation."

It seemed of value, therefore, to reinvestigate the problem and in particular to determine the basal metabolic rate in organic heart disease and whether cardiac overactivity such as may occur in a heart compensating for an organic defect or maintaining an elevated vascular tension is accompanied by increased heat production.

We have studied the metabolic rates obtained under basal conditions in a series of forty-two cases of heart disease including twenty-two patients with valvular lesions, fifteen with hypertension and cardiac hypertrophy, two with congenital heart disease and three with functional tachycardias. A total of 104 metabolic rate determinations was made in these forty-two cases.

7 Hamburger, W. W., and Lev, M. W. Basal Metabolism in Organic Heart Disease with Decompensation, Preliminary Report, *J. A. M. A.* **84**: 587 (Feb. 21) 1925.

8 Lev, M. W., and Hamburger, W. W. Basal Metabolism in Organic Heart Disease. *Am. Heart J.* **1**: 240 (Dec.) 1925.

EXPERIMENTAL RESULTS

The patients in the postabsorptive state were each brought from the ward to the metabolism room in a wheel chair, and were given a minimum of twenty minutes' rest before the test was commenced. The Tissot method was used in all instances. All the results reported represent the findings in at least two successive determinations. Checks were obtained in the analyses of the gases in each instance reported.

We have observed the presence of anxiety and apprehension more frequently among patients with heart disease than in any other class of patients, an experience noted by other workers in this field. It has been found that in persons who do not have heart disease anxiety, fear and worry may give abnormally high metabolic rates. This applies probably even more to patients with cardiac disease than to other groups of cases. Consequently, we have taken special pains to train our subjects by first permitting each to witness another patient being run for metabolism and later, if necessary, have run the cardiac patient once or, in some instances, twice before the actual basal metabolic rate was determined. By such means we have obtained some interesting data which will be referred to later in the article.

In the accompanying table we consider as normal all results between -10 per cent and $+15$ per cent. The respiratory quotient is given in each case.

The patients referred to in the table as having good cardiac reserve were up and about and able to exert themselves moderately without respiratory embarrassment. Those with fair cardiac reserve were comfortable at rest, but were dyspneic on moderate exertion. The patients with poor cardiac reserve usually had enlargement of the liver or slight edema. They were dyspneic on slight exertion but were comfortable while at rest in bed.

COMMENT

Of the forty-two patients studied the heat production was found to be definitely elevated above normal in three cases. These patients all had dyspnea or hyperpnea which, we believe, was responsible for the increased metabolism. However, the possible influence of apprehension in these cases must not be lost sight of. The following case is described to illustrate how the anxiety that cardiac patients sometimes encounter may elevate the metabolism.

A woman, aged 65, with chronic cardiovalvular disease, showed metabolic rates of $+37$ per cent and $+30$ per cent the first and second times, respectively, that such determinations were made. The third and fourth metabolic rates, however, were normal ($+2$ per cent). All four determinations were made within ten days. She stated that she felt nervous during the first two determinations (although there were no outward evidences of such a condition) but more at ease during the third and fourth.

Summary of Findings

Case	Age	Sex	Clinical Diagnosis	Pulse Rate	Blood Pressure	Cardiac Reserve	Dyspnea	Respiratory Quotient	Basal Metabolic Rate	Number of Determinations	Remarks
1	34	♂	Chronic glomerular nephritis, hypertension, cardiac hypertrophy	82	230/110	Good	No	0.81	Normal	2	Nitrogen retention
2	36	♀	Chronic glomerular nephritis hypertension, cardiac hypertrophy, aortic insufficiency	96	250/150	Fair	No	0.72	Normal	4	Nitrogen retention
3	18	♀	Hypertension, cardiac hypertrophy	120	190/110	Fair	No	0.80	Normal	2	
4	17	♀	Hypertension, cardiac hypertrophy	96	190/105	Fair	No	0.75	Normal	2	
5	56	♀	Chronic endocarditis, left hemiplegia, hypertension cardiac hypertrophy	84	175/115	Fair	No	0.80	Normal	4	
6	60	♀	Mitral insufficiency, hypertension, cardiac hypertrophy	80	175/90	Good	No	0.81	Normal	2	Died of cerebral hemorrhage
7	66	♂	Hypertension, cardiac hypertrophy	90	260/110	Good	No	0.86	Normal	2	
8	52	♀	Hypertension, cardiac hypertrophy	82	230/120	Good	No	0.73	Normal	2	Died of cerebral hemorrhage
9	51	♂	Hypertension, premature contractions, cardiac hypertrophy	84	180/90	Good	No	0.82	Normal	2	
10	60	♀	Hypertension, cardiac hypertrophy	60	235/100	Good	No	0.80	Normal	2	
11	15	♀	Persistent tachycardia (functional?)	140	135/75	Good	No	0.75	Normal	2	
12	12	♀	Persistent tachycardia (functional?)	120	125/75	Good	No	0.81	Normal	2	
13	63	♀	Hypertension, mitral stenosis, cardiac hypertrophy, auricular fibrillation	90?	190/90	Poor	Slight	0.83	Normal	2	Lymphema
14	27	♂	Chronic endocardial disease, aortic insufficiency	80	160/60	Good	No	0.76	Normal	2	
15	18	♂	Mitral insufficiency, cardiac hypertrophy	96	100/70	Fair	No	0.91	Normal	2	
16	26	♀	Chronic endocardial disease, mitral stenosis, aortic insufficiency	120	160/90	Poor	No	0.85	Normal	4	Erythema nodosum, enlarged liver, no edema
17	20	♀	Aortic insufficiency, hypertension, cardiac hypertrophy	90	200/140	Good	No	0.82	Normal	2	
18	36	♀	Neurosis, cardiac hypertrophy, kyphoscoliosis	120	120/80	Fair	Slight	0.76	Normal	2	Persistent tachycardia
19	40	♀	Mitral stenosis, auricular fibrillation, cardiac hypertrophy	108	170/90	Fair	No	0.82	Normal	2	
20	24	♂	Mitral stenosis, cardiac hypertrophy	80	110/80	Good	No	0.82	Normal	2	
21	14	♀	Congenital heart disease, cardiac hypertrophy	110	135/80	Good	No	0.79	Normal	2	

22	65	♀	Chronic cardiovascular disease, cardiac hypertrophy, hypertension	103	205/110	Poor	No	0.78	Normal	4	
23	22	♂	Congenital heart disease, cardiac hypertrophy	110	140/80	Good	No	0.75	Normal	2	Enlarged liver, slight edema
24	30	♂	Mitral insufficiency, mitral stenosis, tricuspid stenosis, auricular fibrillation	96?	140/75?	Poor	Slight	0.78	Normal	2	Enlarged liver, slight edema
25	61	♂	Hypertension, cardiac hypertrophy	84	150/90	Poor	Slight	0.80	Normal	8	Enlarged liver, slight edema
26	38	♀	Hypertension, cardiac hypertrophy	116	220/120	Very poor	Yes	0.81	+36%	4	Enlarged liver, edema
27	46	♀	Mitral stenosis, auricular fibrillation, cardiac hypertrophy	110?	145/100?	Very poor	Yes	0.84	+40%	2	Enlarged liver, edema, hy-
28	30	♀	Mitral stenosis, auricular fibrillation, cardiac hypertrophy, hypertension	96?	170/100?	Poor	Slight	0.79	+43%	4	Enlarged liver
29	35	♀	Mitral stenosis, cardiac hypertrophy, auricular fibrillation	63?	140/80?	Poor	Slight	0.81	Normal	2	Enlarged liver, acidosis
30	52	♂	Mitral stenosis, cardiac hypertrophy, auricular fibrillation	108?	190/100?	Poor	Slight	0.80	Normal	2	Enlarged liver
31	60	♀	Chronic cardiovascular disease, cardiac hypertrophy	96	130/85	Fair	Slight	0.76	Normal	2	Enlarged liver
32	40	♀	Mitral stenosis, mitral insufficiency, cardiac hypertrophy, auricular fibrillation	90?	140/90?	Poor	No	0.86	Normal	2	
33	22	♀	Mitral stenosis, premature contractions, cardiac hypertrophy	110?	140/90?	Poor	Slight	0.79	Normal	4	
34	15	♀	Mitral stenosis, aortic insufficiency, auricular fibrillation, cardiac hypertrophy	90?	100/60?	Very poor	Yes	0.80	+29%	2	Hydrothorax, edema
35	51	♂	Hypertension, cardiac hypertrophy, syphilis	106	225/130	Good	No	0.81	+33%	2	
36	11	♀	Mitral stenosis, mitral insufficiency, cardiac hypertrophy	78	135/75	Good	No	0.80	Normal	2	
37	53	♀	Hypertension, cardiac hypertrophy	88	230/130	Good	No	0.78	Normal	2	
38	50	♀	Aortic insufficiency, hypertension, hemiplegia	90	240/140	Fair	No	0.83	Normal	2	
39	49	♀	Hypertension, cardiac hypertrophy	80	240/130	Fair	No	0.81	Normal	2	
40	15	♀	Hypertension, cardiac hypertrophy	78	230/120	Good	No	0.79	Normal	2	
41	26	♀	Mitral stenosis, chronic hypertrophy	88	95/70	Fair	No	0.80	Normal	2	
42	33	♂	Hypertension, cardiac hypertrophy, left hemiplegia	70	180/100	Good	No	0.90	Normal	2	

* In this table, ♂ indicates male, ♀, female

In the remaining thirty-nine cases, we found that organic heart disease unaccompanied by dyspnea at rest does not elevate the basal metabolism

The metabolic results obtained in cardiac disease may in addition be higher than normal by reason of certain sources of error such as the condition of the patient at the time of the test and the method used for its determination. If a patient with reduced oxygen saturation of the arterial blood, which is frequently observed in cardiac disease with or without cyanosis, is suddenly given pure oxygen to breathe, his blood will absorb relatively excessive quantities of this gas. If an oxygen absorption method is used (Benedict apparatus) an untrue and high result will be obtained. Thus, it has been found by comparing results obtained with the Tissot spirometer and the Benedict apparatus that the closed circuit method gave higher readings than the Tissot in cases with "arterial anoxemia."⁹ The possibility exists, therefore, that in at least some of the subjects in whom Hamburger and Lev obtained increased metabolic rates that could not be explained on the basis of dyspnea, there may have been a state of reduced oxygen saturation of the arterial blood at the time the tests were made. They used the Benedict apparatus. Had the open circuit or chamber methods been used these patients' metabolic rates might have fallen within normal limits. We believe these criticisms cast some doubt on the observations reported by Hamburger and Lev. At all events, it is essential that they be confirmed either with the Tissot spirometer or with a method of direct calorimetry before their findings can be considered of significance. As appears from the table, we have been unable to do so using the Tissot apparatus.

Our results are virtually the same as those reported by Peabody, DuBois and their associates. We find that the metabolic rates of persons with organic heart disease, including those with hypertension and cardiac hypertrophy, obtained under basal conditions, fall within the accepted normal limits. High readings are usually due to dyspnea.

We have observed increased basal metabolism in a series of patients with true hypertension (systolic and diastolic) who did not have exophthalmic goiter and who were not dyspneic at the time the metabolic rates were determined. These cases have been reported elsewhere.¹⁰

CONCLUSIONS

The basal metabolic rate in patients with organic heart disease is normal. High readings are usually due to dyspnea.

Cardiac overactivity such as occurs in a heart compensating for an organic heart defect or maintaining an elevated vascular tension does not detectably elevate the heat production.

⁹ King, J. T., Jr. *Basal Metabolism*, Baltimore, Williams & Wilkins Co., 1924.

¹⁰ Boas, E. P., and Shapiro, S. *Diastolic Hypertension with Increased Basal Metabolic Rate*, J. A. M. A. 84: 1558 (May 23) 1925.

THE USE OF SODOKU IN THE TREATMENT OF GENERAL PARALYSIS

A PRELIMINARY REPORT *

H C SOLOMON, M D

Chief of Therapeutic Research, Boston Psychopathic Hospital, Associate in
Psychiatry, Instructor in Neuropathology, Harvard Medical School

A BERK, M D

Assistant in Therapeutic Research, Boston Psychopathic Hospital

M THEILER, M R C S

Assistant in Tropical Medicine, Harvard Medical School

AND

C L CLAY, M D

Senior Assistant Physician, Danvers State Hospital

BOSTON

This is a preliminary report of the use of sodoku in the treatment of general paralysis. The series consists of twelve parietic patients who were inoculated with *Spuochaeta morsus-muris*, the etiologic agent of sodoku. This work was undertaken in an attempt to improve on the malarial method which has been used for eight or nine years in the treatment of general paralysis. It therefore seems advisable to preface the report of our investigations with an account of the treatment of general paralysis by malaria and other febrile producing methods.

In 1917 von Jauregg¹ introduced the malarial method. Since that time it has been quite generally utilized in most of the countries of Europe and also in the United States, the results reported being extremely favorable. The method usually consists of inoculating a patient with malarial blood, which leads to the development of malarial paroxysms. The patient is generally allowed to have from eight to fifteen paroxysms, after which the malaria is cured by quinine. According to the recorded observations in a considerable number of general paralysis patients treated in this manner very good remissions have been obtained shortly after the course of malarial infection. The reports in the literature and our own experience would seem to show that this method does definitely modify the course of general paralysis in a considerable number of cases.

Sodoku is a synonym for rat bite fever.

* From the Boston Psychopathic Hospital, the Department of Tropical Medicine of the Harvard Medical School, and the Danvers State Hospital. Financial assistance was obtained from the Division of Mental Hygiene of the Massachusetts Department of Mental Diseases.

1 Von Jauregg, Wagner. Ueber die Einwirkung der Malaria auf die progressive Paralyse, Psychiat-Neurol Wchnschr 20 132 (Aug 31) 1918.

The original employment of this treatment in the hands of von Jauregg was largely empirical, but was based particularly on his previous experience with the various methods of producing fever in general paralysis patients. In 1887 he published an article² in which he reviewed previous observations tending to show that febrile diseases occurring in general paralysis patients often changed the course of the disease. Observations of the beneficial effect of febrile diseases on various psychoses had been recorded from time to time from the period of Hippocrates and Galen. As a result of these observations, von Jauregg suggested that the inoculation of malaria might be a justifiable means of treating cases of general paralysis, but he did not begin the use of this method until thirty years later. As early as 1889 he used various methods³ of producing fever in general paralysis patients such as by the inoculation of tuberculin, Besredka's typhoid culture, streptococcus and staphylococcus vaccines. He was convinced that these methods, especially the one in which tuberculin was employed, were of considerable value and was supported in his belief by several investigators, notably Pilcz.⁴

Other observations were added tending to show the value of the occurrence of fevers in the modification of syphilis of the nervous system. For instance, it was stated that in certain countries such as Indo-China,⁵ where both syphilis and malaria are endemic, cases of paretic and tabetic neurosyphilis are quite rare. This led to the hypothesis that the malarial infection somehow protects the central nervous system of the individual from invasion by *Spirochaeta pallida*. Mattauschek and Pilcz,⁶ in the now classical analysis of the histories of 4,134 Austrian army officers who had become infected with syphilis, pointed out that the patients who developed an acute febrile disease, such as pneumonia, typhoid and the like, during the first year of syphilis, did not develop neurosyphilis in the later course of their lives. On the contrary, those patients who did develop neurosyphilis, practically without exception, did not have acute febrile diseases during the first year of syphilis.

2 Wagner, Julius. Ueber die Einwirkung fieberhafter Erkrankungen auf Psychosen, *Jahrb f Psychiat* 7 94, 1887.

3 Von Jauregg, Wagner. Ueber die Behandlung der progressiven Paralyse, *Wien med Wchnschr* 59 2124 (Sept 11) 1909, Ueber die Behandlung der progressiven Paralyse mit Bakterientoxinen, *Wien klin Wchnschr* 25 61 (Jan 4) 1912.

4 Pilcz, A. Zur Prognose und Therapie der Paralysis progressive, *Ztschr f d ges Neurol u Psychiat* 4 457, 1911.

5 Bercovitz, N. Neurosyphilis and Malaria in Hainan (China), letter to editor, *J A M A* 82 1713 (May 24) 1924.

6 Mattauschek, E., and Pilcz, A. Beitrag zur Lues-Paralyse-Frage, *Ztschr f d ges Neurol u Psychiat* 8 133, 1912. Zweite Mitteilung uber 4, 134 katamnestisch verfolgte Falle vonluetischer Infection, *Ztschr f d ges Neurol u Psychiat* 15 608, 1913.

Fortified by these observations and previous experience with febrile producing methods, von Jauregg¹ in 1917 started treating cases of general paralysis by the inoculation of malaria.

If one accepts the conclusion that malaria does modify the course of general paralysis, it is desirable to have some explanation of the way this is brought about. We can only theorize as to the explanation of this effect and none of the theories are convincing. However, two hypotheses that have been suggested may be mentioned. One is that the repeated high temperature reactions produced by the malaria are lethal for the spirochete,⁷ another, that immunity reactions produced by the acute disease are effective against the etiologic agent of general paralysis.⁸

The advantages of inoculating the parasite of malaria as a febrile producing method may be summarized as follows:

1. Frequent high temperatures are produced.
2. A great majority of people are susceptible to the disease.
3. The rises in temperature recur at short intervals.
4. The disease is readily controlled by quinine.

There are, however, a number of disadvantages to the use of malaria in treatment:

1. It is not practical to keep the living organism either in culture or in a laboratory animal but, on the contrary, the disease must be transmitted from patient to patient. This means, if one is to carry on the work, that one must always have available a patient carrying the plasmodia in his blood. In the communities where malaria is not endemic, this is only possible if one is treating a large group of patients and can keep the strain going continuously. This is a great disadvantage and means that the treatment may not be available in many communities.

2. Malaria causes severe reactions and leads to a certain mortality. Due to the destruction of red cells, a considerable degree of anemia is usual. Jaundice is not an infrequent complication.

3. There is the possibility of inoculating the estivo-autumnal form by accident and in association with the tertian parasite.

4. Under most circumstances it is necessary to carry on the inoculation from patient to patient, which means the carrying over of syphilitic blood.

5. Some patients are not susceptible to malaria, some have a limited number of paroxysms which then spontaneously cease.

7 Weichbrodt, R., and Jahnel, F. Einfluss hoher Korpertemperaturen auf die Spirochäten und Krankheitserscheinungen der Syphilis. *Tierexperiment*, Deutsche med. Wchnschr. **45** 483 (May 1) 1919.

8 Plaut, F. Neuere Probleme der Paralyse und Tabes-therapie, Deutsche med. Wchnschr. **45** 1321 (Nov. 27) 1919.

In order to improve on malarial treatment, Plaut⁹ introduced the method of inoculating patients with relapsing fever, which is less severe in its effect on patients than is malaria, and as laboratory animals are susceptible to infection with the organisms causing the relapsing fevers, they can be always available. Plaut also suggests a theoretical advantage of employing relapsing fever in that the organism of this disease is much more nearly related to *Spirochaeta pallida* than is the plasmodium of malaria, thus offering more likelihood of effective immunity reactions. However, there also are great disadvantages in the use of relapsing fever. The paroxysms of fever are likely to be separated by many days or weeks, so that at the best the treatment must take a considerable period of time. Relapsing fever, which is a self-limited disease, not infrequently ends before many attacks of fever have occurred. Furthermore, in Plaut's own experience, arsphenamine, which is supposed to be a specific for this disease, apparently was without effect so that the cases had necessarily to run their course. This is a fundamental objection as at times it is apparently impossible to control the disease. Several attempts have been made in the United States to utilize relapsing fever in the treatment of general paralysis but no strains of sufficient virulence have been obtained. We have tried to increase the virulence of the strain at our disposal, but have not been successful and we have only succeeded in getting the patients to have two, three or four mild rises in temperature. We have therefore sought for another organism that would have as many of the favorable characteristics as possible and as few of the unfavorable.

Spirochaeta morsus-muris, the specific organism of sodoku, meets most requirements. Sodoku is a disease fairly well known in Japan and has been occasionally recognized in the United States, as well as in most other countries of the world. Infection is produced by the bite of a rat or several other animals infected with *Spirochaeta morsus-muris*.

The disease produces a number of symptoms suggestive of syphilis. At the locus of the rat bite in the course of from one to fifty days (average, from five to ten days) a sore, suggestive of a chancre, appears. This primary lesion is covered by a black or reddish purple scab and has an average diameter of 2.5 cm. A lymphangitis from the sore to the neighboring lymph glands occurs with redness and slight tenderness. The regional lymph glands, as well as some at a distance, become enlarged and tender. The spirochetosis becomes generalized as the organisms are carried into the blood stream. After from five to

⁹ Plaut, F, and Steiner, G. Recurrensinfektionen bei Paralytikern, Ztschr Neurol u Psychiat Orig 53 103, 1920

fifteen days fever occurs, and skin lesions of various types, quite similar to those which characterize the secondary period of syphilis, appear over various parts of the body, particularly the trunk. The temperature, which rises from 104 to 105.5 F or higher, is of the intermittent type dropping after a period of a few hours to normal. This rise and fall is repeated from time to time, often at daily or bi-daily intervals. The disease is said to be self-limited, but often continues with febrile exacerbations for a period of several months. It does, however, quickly respond to arsphenamine. In the disease acquired from the rat, the mortality, even in the untreated cases, is small and, as noted, may be readily controlled by arsphenamine.

Though sodoku has been recognized for a long time as a clinical entity, it is only in recent years that the etiology of the disease has been revealed. Futaki and his collaborators¹⁰ were the first to describe a spirochete. Before this, however, Hata¹¹ had surmised that the causative agent was a spirochete and had introduced arsphenamine with brilliant curative results. The work of the Japanese has been confirmed in various countries of the world. *Spirochaeta morsus-muris* is a short but rather thick spiral organism. The curves are sharp and very regular. The body of the organism terminates in a point at either end, from each of which typically rises one flagellum (fig 1). The extraordinary rapidity of movement of this organism is due to the flagella. The accounts of the morphology of the spirochetes observed by various investigators differ considerably, particularly as to the average length and the average number of spirals per organism. The points of difference, however, are not of great importance, for it has been shown by Robertson¹² that the average length varies considerably from time to time in the same strain. *Spirochaeta morsus-muris* can be kept indefinitely in laboratory animals. Mice and rats, when infected, show no signs of illness but harbor the organism in the blood. Guinea-pigs show signs that are comparable to the disease as observed in human beings. Thus, there is a primary lesion at the site of inoculation, followed by enlargement of the inguinal lymphatic glands, and fever. Alopecia is always a marked late manifestation in guinea-pigs but has not been observed in man. Our strain also invariably causes inflammation and later induration of the scrotum or labia.

10 Futaki, K., Takaki, J., Tanguchi, T., and Osumi, S. The Cause of Rat Bite Fever, *J. Exper. Med.* **23** 249 (Feb.) 1916, *Spirochaeta Morsus-Muris*, N. Sp., the Cause of Rat Bite Fever, *J. Exper. Med.* **25** 53 (Jan.) 1917.

11 Hata, S. Salvarsantherapie der Rattenbisskrankheit in Japan, *Munchen med. Wchnschr.* **59** 854, 1912.

12 Robertson, A. Observations on the Causal Organism of Rat Bite Fever in Man, *Ann. Trop. Med.* **18** 157 (Aug.) 1924.

The strain of spirochetes used in these experiments was obtained by one of us (M T) in November, 1923,¹³ from a typical case of rat bite fever in a baby. It has been maintained in experimental animals since that time. The pathogenicity for laboratory animals has been the subject of another article to be published.¹⁴ The strain has been passed through two mice, two rabbits and four guinea-pigs, a total of eight passages spread over a period of twenty months. The virus was kept for eleven months in one of the mice.

The material used for human inoculations consisted of the citrated blood taken under aseptic precautions from the heart of an infected guinea-pig or rat. In every case the blood was previously examined by dark field for spirochetes and two mice and two guinea-pigs were inoculated immediately afterward with the material used for human inoculations. All the animals inoculated with the material used for the human experiments developed typical signs of experimental rat bite fever with spirochetes in their blood.

The clinical effects produced by *Spirochaeta morsus-muris* seem to us to offer more favorable and fewer unfavorable characteristics than does malaria. The organisms can be kept in a laboratory animal, available for inoculation at any time. The patient's reaction is less severe than it is with malaria, although a fair degree of fever is obtained. It is readily controlled by arsphenamine. There is evidence of the production of immune bodies which, at least from the theoretical standpoint, may be of some importance.

Because of the facts enumerated, it seemed to us advisable to use this method in the treatment of general paralysis. The first point to be determined was the possibility of artificial inoculation. In a preliminary study three general paralysis patients were inoculated intradermally. In each instance there was definite evidence of the development of sodoku. A detailed account of one of these cases is given here (case 1). The general course in these cases was much the same, although varying in certain details. In the course of from three to five days a redness and swelling occurred at the site of inoculation, which was followed by the formation of a chancre-like sore.

These inoculations were made on the anterior surface of the right thigh. The lymphatics leading from this point to the groin became reddened and moderately tender. The regional lymph glands became moderately enlarged, to the size of a pea, and slightly tender.

About three days after the development of the sore, attacks of fever occurred, the temperature rising to 102 to 104 or 105 F, remain-

13 Shattuck, G C, and Theiler, M. Rat Bite Disease in the United States with Report of a Case, *Am J Trop Med* 4 453 (Sept) 1924.

14 Theiler, M. Experimental Rat Bite Fever, *Am J Trop Med*, to be published.

ing up for a few hours to a couple of days and then descending. Subsequent rises occurred at varying intervals from a day to three or four days. A number of attacks of fever occurred during a period of weeks and then apparently the temperature ceased spontaneously, or was stopped by arsphenamine. This tendency for the fever to cease and then recur is suggestive of what occurs in malaria. In sodoku during the period of the fever, the lymph glands in various portions of the body become enlarged. At the same time skin lesions appear.

The effect of arsphenamine on the disease is extremely striking. The clinical manifestations disappear with great rapidity. Thus, in the

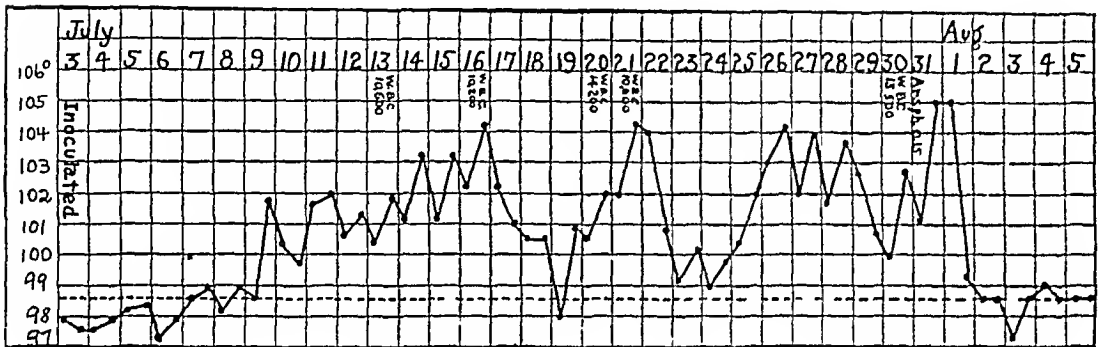


Chart 1 (case 1) —Temperature curve

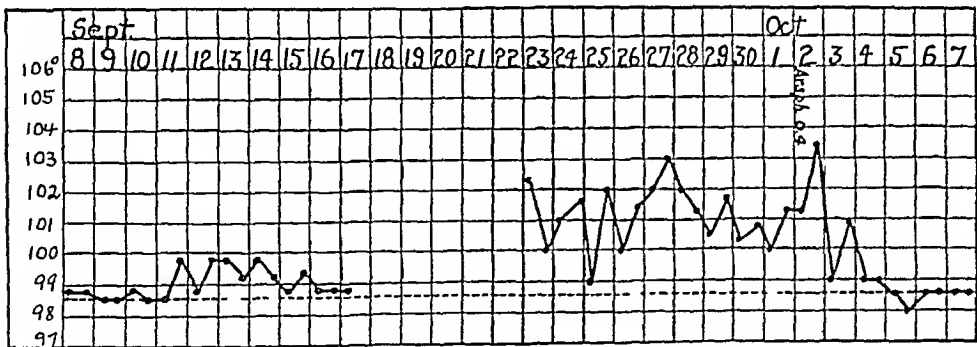


Chart 2 (case 1) —Temperature curve

case of patient 1, 0.15 Gm of arsphenamine produced what appeared to be a Herxheimer reaction or therapeutic shock followed by healing of the lesions. The temperature, which was about 101.5 F at the time of the arsphenamine injection, rose to over 105 F accompanied by a chill, the temperature then dropped to normal within several hours and there was no subsequent rise for some weeks (chart 1). The same therapeutic effect was obtained with each of the other patients. In the case of patient 1, two injections of 0.15 Gm of arsphenamine were given and the clinical course closely observed. The temperature remained normal for fifty-two days and then again rose above normal (chart 2).

At the same time a localized lesion appeared. After ten days he was given another injection of arsphenamine and as on the previous administration of arsphenamine, the manifestations rapidly disappeared. Repeated injections were given and no further relapses have occurred although a period of several months has elapsed.

The other patients received a number of injections of arsphenamine and no true relapses occurred after treatment, although patient B developed some redness and tenderness at the point of the primary lesion during a short intermission of treatment.

The blood serum of these patients during the course of the disease and also subsequently to the apparent cure by arsphenamine contained immune bodies and rapidly killed in vitro *Spirochaeta morsus-muris*, thus indicating that the patients had not only been successfully inoculated, but had developed immune bodies which they carried in their blood for a long period.

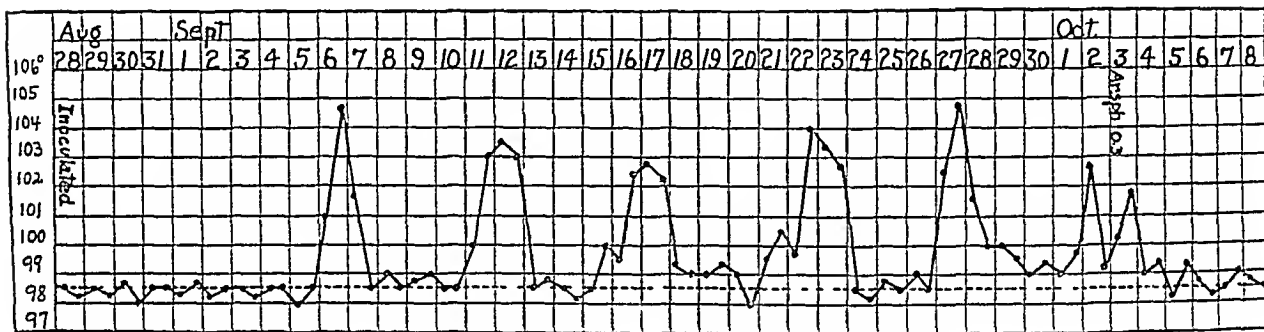


Chart 3 (case 2) —Temperature curve

From these three cases we feel justified in drawing the following conclusions:

1. Sodoku can be artificially transmitted from animal to man.
2. The disease produces a generalized reaction with the production of fever and antibodies.
3. It is not dangerous to the life of the patient and is easily controlled by arsphenamine.

By intravenous inoculation, if care is taken not to allow the blood to get into the skin at the point of the venipuncture, no primary sore is produced. Eight patients were treated by intravenous inoculations. One patient died of general paralysis before the incubation period had passed. The remaining seven patients all showed clinical evidences of sodoku and the blood serum from each patient gave positive spirocheticidal tests. At the end of from one to three weeks fever occurs and later skin manifestations make their appearance (chart 3). There is, at times, a generalized glandular enlargement. The subsequent

course of the malady is much the same as that in which the inoculation is made intradermally. Infection produced by intravenous inoculation is controlled by arsphenamine just as promptly as when the infection is given intradermally. The amount of infective blood given intravenously varied from 0.1 to 1 cc of rat or guinea-pig blood. There was no appreciable difference in the clinical course of the disease dependent on the amount of blood inoculated.

Sudoku was successfully produced in two patients subsequent to malaria. In one patient malaria was successfully transmitted after the patient had sudoku. In another patient an attack of relapsing fever was produced by injecting blood containing spirochetes of relapsing fever after the patient had had sudoku and still had immune bodies in his blood. This indicates that sudoku may be used before or after malaria, thus making it possible to use both methods in the treatment of a general paralysis patient.

REPORT OF CASES

CASE 1—A, a white man, a dyer, aged 40, married, of German extraction, was admitted, June 6, 1925, because of confusion and disorientation. His past history was of no importance. His life was practically uneventful until suddenly in February, 1925, he had a "nervous breakdown." In June, he was not heard from for about a week until his wife received a call from the police. His brother secured his release by the police and had him sent to the Boston Psychopathic Hospital.

On admission the patient was overtalkative, easily distracted and grandiose. His pupils were sluggish, there were tremors of the tongue and slurring speech. His memory was poor, and he had ideas of grandeur pertaining to large amounts of money. The physical examination revealed signs characteristic of general paralysis, and the serology was strongly positive, showing the following: Wassermann reaction of serum, positive; Wassermann reaction of fluid, positive; cells, 48 per cmm; globulin, 2+; total protein, 70 mg per hundred cubic centimeters; sugar, 55 mg per hundred cubic centimeters; colloidal gold reaction, 5554420000. A diagnosis of general paralysis was made.

July 5, he was inoculated intradermally on the anterior surface of the right thigh under aseptic precautions with 1 cc of citrated blood taken from a guinea-pig that presented typical signs of sudoku, and the blood of which revealed numerous spirochetes. From the same material, two guinea-pigs were inoculated immediately afterward, and in the course of time developed typical experimental rat bite fever with the causative organisms in the blood.

At the time of inoculation, the inguinal region revealed on examination a few small glands. The intradermal injection produced an indurated area about 3 cm in diameter, without redness.

Three days later, the skin over the indurated area assumed a bluish color, involving an area 1 cm in diameter. There was no temperature, and the glands remained unchanged. During the following two days the bluish tinge turned to a pink with redness surrounding it. Induration was present, and it was sore.

On the sixth day following inoculation, the temperature rose to 101.8 F. The patient complained of general malaise. The indurated area increased in size and became redder and more tender. The inguinal glands felt harder.

On the seventh day the temperature was still elevated. The glands were larger and harder. At the margin of the lesion a small bleb about 0.5 cm in diameter appeared.

Later the patient complained of pain throughout the body, especially in his bones and joints, stating "it is just like the grippe." Several more blebs appeared around the primary lesion and the area of induration and redness became larger. The center of the lesion turned to a dark blue and broke down and exuded serum. The area of induration and inflammation increased in size rapidly, as did the glands. Smears were made from the exudation and were examined by dark field and stained with Giemsa stain but no spirochetes were seen.

On the twelfth day the glands became tender for the first time, although previous to this they were large and hard but not painful. The temperature rose to above 103 and the patient complained of general malaise again. The center of the inflamed area became gangrenous and formed a thick black eschar. Lymphangitis was present. The next day the temperature reached 104.4, and the white blood count was 10,200. Later, the temperature dropped to normal.

On the seventeenth day several small circular well defined elevated spots about 1 cm in diameter appeared over the chest and left thigh. A gland puncture was performed and the substance was injected into two mice. The gangrenous portion began to separate from the healthy tissue and formed a round, well defined border. On the flexor surface of the left forearm a hard nodule presented itself, slightly red and tender. At this point venipuncture had been performed eight days before.

The following day many more spots appeared. The temperature rose to 104. The next day the temperature dropped, and the spots lost their deep rose color, became less defined, flattened out, and some had disappeared almost entirely. For the following day or so the temperature was normal and the spots were hardly discernible. Again the temperature rose and the spots reappeared, assuming a size, shape and appearance similar to those of the previous crop, but more spots appeared over the face, scalp, legs, abdomen and back.

On the twenty-eighth day the patient was given 0.15 Gm of arsphenamine intravenously. In the evening the temperature rose to 105 and remained elevated until the following morning when it reached normal. During the height of the fever, the patient became delirious and excited and had to be kept in bed. This was similar to the so-called Herxheimer reaction or therapeutic shock as seen in the treatment of syphilis.

The day following the intravenous medication, the temperature became normal, the spots practically disappeared, and the ulcer revealed granulating tissue. At this time the serology was: Wassermann reaction of blood serum, positive, Wassermann reaction of spinal fluid, positive, globulin, 1+, cells, 12 per cmm, colloidal gold reaction, 3321000000.

Three days later the patient was given another dose of 0.15 Gm of arsphenamine, and on the next day the plug of gangrenous tissue came away of its own accord and the red spots entirely disappeared, leaving an occasional desquamating area where a spot had been.

The next day the ulcer was perfectly clean and free of necrotic tissue. As the days went by the ulcer healed in a fairly rapid manner.

September 11, the patient complained of a head cold for which he was treated, and he apparently recovered. Four days later there appeared a small area of erythema on the lower eyelid in the same area where one of the characteristic red spots previously had appeared, and the left side of the nose swelled. The swelling extended to the left cheek and then to the glands at the angle of the jaw. The temperature ranged from 99 to 102 F.

Fifteen days following the first appearance of the swelling of the nose, the patient was given 0.2 Gm sulpharsphenamine intravenously, and later 0.4 Gm arsphenamine. Three-quarters of an hour after the second injection, he developed a chill lasting twenty-five minutes and the temperature rose to 102.2. Forty-eight hours later, the facial swelling and the enlarged glands had practically disappeared. Several days later he was working around the ward. He received subsequent weekly intravenous arsphenamine injections and there were no further relapses. The serology at this time revealed some improvement.

The patient was discharged from the hospital as improved and capable of taking care of himself. When last heard from, about five months later, no relapses had occurred.

CASE 2—D, a white man, aged 34, married, an accountant, was admitted to the Boston Psychopathic Hospital, June 13, 1925, on the complaints of acting peculiarly, memory lapses, stammering speech, excitement and incoherence. The past history was of no importance. The onset of the illness was gradual, beginning with a physical decline in the spring of 1924. He became thin and was easily tired out, then became irritable and did not get along well with his family. On account of this, he left home and nothing was heard from him until June 5, when his wife was called to the Massachusetts General Hospital to see her husband. She was advised to take him to the Boston Psychopathic Hospital.

Here, the diagnosis of general paralysis was made on the history, neurologic signs, including Argyll-Robertson pupils, hyperactive reflexes, slurring speech, tremors of facial muscles, the mental symptoms of disorientation, poor memory, deterioration, and the serologic findings, which showed the following results: Wassermann reaction of blood serum, positive, Wassermann reaction of spinal fluid, positive, globulin, 3+, cells, 15 per cmm, total protein, 167 mg per hundred cubic centimeters, and colloidal gold reaction 5554332000.

The patient was treated by malaria and allowed to have eight paroxysms. There was no improvement and the spinal fluid examination following the malarial treatment was but little changed.

August 28, he was inoculated intravenously with 0.1 cc of blood.

September 6, the temperature rose to 104.6, and the next day was normal, making an incubation period of nine days. On the eighth day there appeared at the site of the intravenous inoculation at the bend of the right elbow an area of redness and induration the size of a half-dollar.

The patient was transferred to the Westboro State Hospital, September 11. He ran an irregular temperature (chart 3) until given eight intravenous injections of 0.3 Gm of arsphenamine, following the first of which the temperature became normal and the disease was apparently cured.

DIAGNOSIS BY ANIMAL INOCULATIONS

The diagnosis of naturally acquired rat bite fever is usually a simple matter if there is a history of a bite followed by the development of lymphangitis, lymphadenitis, a relapsing temperature, and an exanthem. In atypical cases, or when there is no history of a bite, the disease probably is often not diagnosed. The demonstration of the causative organism is therefore of great diagnostic value. In two of the foregoing cases we endeavored to demonstrate the spirochete by the inoculation of experimental animals with blood taken from the patient. For these inoculation experiments we used mice and guinea-pigs. Both animals are very susceptible to the infection. We preferred guinea-pigs because the blood of these animals is normally free from spirochetes, whereas mice are often infected with a spirochete morphologically indistinguishable from the *Spirochaeta morsus-muris*. Before using our mice we therefore examined their blood by the dark-field several times to exclude a natural infection. Blood was withdrawn into a solution of sodium citrate in the usual manner from the patient's veins and about a half-hour afterward inoculated either subcutaneously or intra-

peritoneally into animals. Whenever possible the animals were inoculated with blood taken as soon as the patient's temperature began to rise. Of six guinea-pigs inoculated with the blood from patient 1, only one developed typical signs of infection with spirochetes in the blood. This guinea-pig was injected subcutaneously with 2.5 cc of the patient's blood taken on the seventeenth day after inoculation when the patient's temperature was rising at the commencement of his second paroxysm of the fever. The record of this guinea-pig is briefly as follows. One week after inoculation the guinea-pig showed an indurated area about 2 cm long and 1 cm wide at the site of injection. There was a well defined ulcer about 0.5 cm in diameter over the center of the indurated area. Serum squeezed out of this ulcer was examined by the dark field, but no spirochetes were seen. The inguinal lymph glands became distinctly enlarged. On the fourteenth day spirochetes were first observed in the blood and gradually became more numerous on the succeeding days. This guinea-pig eventually developed the typical disease, with inflammation of the vulva and supralabial and circumocular alopecia. Blood from this guinea-pig was withdrawn on the thirty-ninth day and injected into patient 2 (chart 3).

The record of the guinea-pig that was inoculated at the same time and with the same amount of blood as the one described above is worth reporting. This animal likewise developed an indurated area at the site of inoculation and enlarged lymph glands. At no time, however, were spirochetes demonstrable in the blood. Mooser¹⁵ has shown that *Spirochaeta morsus-muris* can produce a latent infection in guinea-pigs. That is, the guinea-pigs fail to develop clinical symptoms of the infection, but the organism can be recovered from them many weeks afterward by the implantation of the inguinal lymph nodes into other guinea-pigs. Unfortunately, Mooser's work was published too late for us to use his method to determine whether the guinea-pig described above was infected or not. On account of the fact that several of our guinea-pigs developed the same lesions, but at no time were spirochetes present in the blood, we feel that possibly in those cases we were dealing with a latent infection. Of the six guinea-pigs injected with blood from patient 1, one died a few days after inoculation, the one described above developed the typical disease, three developed enlarged inguinal lymph glands, and one remained entirely negative. Two of the guinea-pigs that developed what may be a latent infection were injected with blood taken on the second day of fever, when presumably the organisms were present in the patient's blood.

15 Mooser, H. Experimental Studies with a Spiral Organism Found in a Wild Rat, *J. Exper. Med.* **39** 589 (April) 1924, Experimental Studies with a Spiral Organism Found in a Wild Rat and Identical with the Organism Causing Rat Bite Fever, *J. Exper. Med.* **42** 539 (Oct.) 1925.

Two guinea-pigs that were inoculated with the serum expressed from the primary lesion of patient 1 remained negative. Of two mice injected with the fluid aspirated from the enlarged inguinal lymph gland, one developed the infection. Spirochetes were first seen in the blood of this mouse on the tenth day.

Seven guinea-pigs were inoculated with blood taken from patient B. Five of these remained in every respect normal. Two developed what is probably a latent infection, namely, an indurated area at the site of inoculation and enlarged lymph glands.

It will thus be seen that the diagnosis of sodoku by the demonstration of the causative organism either directly or by animal inoculation may be very difficult. Fortunately, there is a reliable serologic reaction. Futaki and his co-workers¹⁰ have shown that when the blood serum from a convalescent patient with sodoku is mixed with blood containing *Spirochaeta morsus-muris*, the spirochetes immediately lose their motility and become disintegrated. During our rabbit experiments we became familiar with this reaction and convinced ourselves of the reliability of this test. The serums of all our patients were tested by this method and all showed spirocheticidal properties. In every case the spirochetes lost their motility in a few minutes and could no longer be found. The protocol of one of these tests follows.

Serum from patient 1 taken the day before he received an injection of arsphenamine was thoroughly mixed in a capillary pipet with an equal amount of guinea-pig's blood showing numerous spirochetes. This was immediately examined by the dark field. Three minutes after mixing most of the spirochetes were dead and the active movements of the remainder had ceased, each organism remaining at one spot and occasionally showing a convulsive movement. Seven minutes after mixing all the organisms were dead. The control in which normal serum was used showed active motility of the spirochetes for more than a half-hour after mixing.

The spirocheticidal action of the serum of patient 1 also was tested by means of Pfeiffer's phenomenon. A mixture containing 0.5 cc of the patient's serum and 0.5 cc of guinea-pig blood containing numerous spirochetes was injected into the peritoneal cavity of a guinea-pig. Small quantities of fluid were withdrawn from the peritoneal cavity at short intervals and examined under the dark field. In fluid withdrawn seven minutes after injection, only one motile spirochete was seen. Fluid withdrawn after this was always negative. In the control guinea-pig, which was injected the same way except that normal serum was used, there was no loss of motility after one hour.

RESULT OF TREATMENT

It is far too early to attempt to evaluate the therapeutic results of this treatment. At least several years must elapse with a considerable group of patients under treatment and observation. It is even too early to formulate the true value of the malarial treatment. This report is presented to call attention to the possibilities of this method of treatment in producing fever which can be used under circumstances similar to

those in which the malarial or relapsing fever methods have been advocated. However, we do feel justified in stating that clinical and serologic improvement has taken place in some of the patients treated by sodoku, a fact that is at least suggestive of the therapeutic value of the method.

SUMMARY

Sodoku is a disease produced by *Spirochaeta morsus-muris*, characterized by repeated attacks of fever, glandular enlargement and skin lesions, tending to spontaneous recovery after a period of weeks or months. Arsphenamine is apparently a specific therapeutic agent. Immune bodies are formed which offer a means of diagnosis by spirocheticidal tests. The organisms can be maintained in laboratory animals, e. g., rats, mice, guinea-pigs. On theoretical grounds it offers possibilities for the treatment of general paralysis similar to malaria and relapsing fever. Sodoku can be transferred to the human by either intradermal or intravenous inoculation of blood of an infected animal. The intravenous inoculation seems preferable because it avoids the formation of the primary lesion and lymphangitis which results from successful intradermal inoculation. The artificially produced disease is similar in its clinical manifestations to the naturally acquired disease, producing repeated paroxysms of fever of from 102 to 105 F, and is readily controlled by arsphenamine.

As a therapeutic method it has theoretical possibilities equal to malaria. In addition, there are a number of practical advantages over malaria. The organism can be maintained in laboratory animals and is thus always available for use, which obviates the necessity of transmitting human blood or having on hand a case of human infection. The disease is less debilitating to the patient than malaria. A further value is that it can be given to patients who are more or less immune to malaria. It is also available as an addition to the malarial therapy and may be given either before or after malaria without any evident modification of the clinical course of either condition.

ACUTE COCAINE POISONING AND ITS TREATMENT IN THE MONKEY (MACACUS RHESUS) *

A L TATUM, MD

AND

K H COLLINS, BS

CHICAGO

In a previous study of acute experimental cocaine poisoning and its treatment ¹ we reported the following observations from experiments on the dog and the rabbit

1 Death in acute poisoning from the hypodermic injection of cocaine hydrochloride is due to respiratory failure

2 By the intravenous administration of appropriate hypnotics, e g , barbitol sodium (barbitalum soluble, U S P X) with paraldehyde, the minimal lethal dosage of cocaine was raised from approximately 100 mg per kilogram to 150 mg per kilogram in the rabbit, and from approximately 26 mg per kilogram to 65 mg per kilogram in the dog. Convulsions ceased immediately during the injection of the hypnotics

3 The convulsions caused by cocaine are largely of cortical origin, this disturbance contributes or is parallel to the more direct drug injury of the medullary centers, particularly the respiratory center. If the cortical manifestations of cocaine poisoning were controlled by hypnotics it was found that the medullary centers were far more resistant than in uncontrolled instances, thus accounting largely for the increased tolerance in acute poisoning

4 The longer the convulsions are permitted to continue the greater is the danger of medullary failure

5 Artificial respiration as a means of treatment of cocaine poisoning in the rabbit was quite satisfactory but entirely inefficient in the dog. Hence, in the higher mammal, the dog, asphyxia due to convulsions cannot be held responsible as the cause of death

6 The dog was initially much more susceptible to cocaine poisoning than the rabbit and was correspondingly more amenable to hypnotic drug treatment, forming an interesting parallelism with or dependence on brain development

* From the laboratory of pharmacology of the University of Chicago

* This work was supported in part by a grant from the therapeutic research fund of the American Medical Association

1 Tatum, A L , Atkinson, A J , and Collins K H. Acute Cocaine Poisoning, Preliminary Report of Experimental Study, J A M A 84 1177 (April 18) 1925, J Pharm & Exper Therap 26 325, 1925

those in which the malarial or relapsing fever methods have been advocated. However, we do feel justified in stating that clinical and serologic improvement has taken place in some of the patients treated by sodoku, a fact that is at least suggestive of the therapeutic value of the method.

SUMMARY

Sodoku is a disease produced by *Spirochaeta morsus-muris*, characterized by repeated attacks of fever, glandular enlargement and skin lesions, tending to spontaneous recovery after a period of weeks or months. Arsphenamine is apparently a specific therapeutic agent. Immune bodies are formed which offer a means of diagnosis by spirocheticidal tests. The organisms can be maintained in laboratory animals, e. g., rats, mice, guinea-pigs. On theoretical grounds it offers possibilities for the treatment of general paralysis similar to malaria and relapsing fever. Sodoku can be transferred to the human by either intradermal or intravenous inoculation of blood of an infected animal. The intravenous inoculation seems preferable because it avoids the formation of the primary lesion and lymphangitis which results from successful intradermal inoculation. The artificially produced disease is similar in its clinical manifestations to the naturally acquired disease, producing repeated paroxysms of fever of from 102 to 105 F., and is readily controlled by arsphenamine.

As a therapeutic method it has theoretical possibilities equal to malaria. In addition, there are a number of practical advantages over malaria. The organism can be maintained in laboratory animals and is thus always available for use, which obviates the necessity of transmitting human blood or having on hand a case of human infection. The disease is less debilitating to the patient than malaria. A further value is that it can be given to patients who are more or less immune to malaria. It is also available as an addition to the malarial therapy and may be given either before or after malaria without any evident modification of the clinical course of either condition.

ACUTE COCAINE POISONING AND ITS TREATMENT IN THE MONKEY (MACACUS RHESUS) *

A L TATUM, M D

AND

K H COLLINS, B S

CHICAGO

In a previous study of acute experimental cocaine poisoning and its treatment¹ we reported the following observations from experiments on the dog and the rabbit

1 Death in acute poisoning from the hypodermic injection of cocaine hydrochloride is due to respiratory failure

2 By the intravenous administration of appropriate hypnotics, e g , barbitol sodium (barbitalum soluble, U S P X) with paraldehyde, the minimal lethal dosage of cocaine was raised from approximately 100 mg per kilogram to 150 mg per kilogram in the rabbit, and from approximately 26 mg per kilogram to 65 mg per kilogram in the dog. Convulsions ceased immediately during the injection of the hypnotics

3 The convulsions caused by cocaine are largely of cortical origin, this disturbance contributes or is parallel to the more direct drug injury of the medullary centers, particularly the respiratory center. If the cortical manifestations of cocaine poisoning were controlled by hypnotics it was found that the medullary centers were far more resistant than in uncontrolled instances, thus accounting largely for the increased tolerance in acute poisoning

4 The longer the convulsions are permitted to continue the greater is the danger of medullary failure

5 Artificial respiration as a means of treatment of cocaine poisoning in the rabbit was quite satisfactory but entirely inefficient in the dog. Hence, in the higher mammal, the dog, asphyxia due to convulsions cannot be held responsible as the cause of death

6 The dog was initially much more susceptible to cocaine poisoning than the rabbit and was correspondingly more amenable to hypnotic drug treatment, forming an interesting parallelism with or dependence on brain development

* From the laboratory of pharmacology of the University of Chicago

* This work was supported in part by a grant from the therapeutic research fund of the American Medical Association

1 Tatum, A L , Atkinson, A J , and Collins, K H. Acute Cocaine Poisoning, Preliminary Report of Experimental Study, J A M A **84** 1177 (April 18) 1925, J Pharm & Exper Therap **26** 325, 1925

In view of these facts the next logical step would naturally be a study of the same phenomena in still higher forms of life and for this purpose the monkey (*Macacus rhesus*) was chosen

PROTOCOLS

EXPERIMENT 1—Monkey, weight, 33 Kg

10 26 a m Injected 40 mg of cocaine hydrochloride per kilogram, subcutaneously

10 30 a m Animal was delirious, wild

10 40 a m Animal had tremors in the legs

10 47 a m Animal had violent clonic convulsions

10 48 a m Started intravenous injection of 70 mg of barbitol sodium per kilogram in 35 cc of saturated solution of paraldehyde in saline solution per kilogram Immediate cessation of convulsions, excellent muscle relaxation, deep sleep

12 00 Beginning to waken

1 10 p m Able to sit up

1 30 p m Drinking water

3 30 p m Ate a banana

One month later the animal was still perfectly normal in appearance

EXPERIMENT 2—Monkey, weight, 56 Kg

10 59 a m Subcutaneous injection of 60 mg of cocaine hydrochloride per kilogram of body weight

11 05 a m Animal had violent clonic convulsions

11 07 a m Intravenous injection of 35.6 mg of barbitol sodium per kilogram in 175 cc of saturated solution of paraldehyde in saline solution per kilogram Immediate cessation of convulsions Respiration stopped temporarily but returned on artificial respiration

11 40 a m Animal apparently in excellent condition

12 40 p m Tremors appeared in the legs

12 45 p m Respiration was labored, then became weaker, finally ceasing altogether Artificial respiration was maintained for over an hour, when the heart finally ceased beating

2 00 p m Animal died

EXPERIMENT 3—Monkey, weight, 58 Kg

9 50 a m Injected subcutaneously 60 mg of cocaine hydrochloride per kilogram of body weight

9 55 a m Animal had violent clonic convulsions

10 01 a m Gave 70 mg of barbitol sodium per kilogram in 35 cc of saturated solution of paraldehyde in saline solution per kilogram Immediate cessation of convulsions, deep sleep

11 45 a m Beginning to waken

12 05 Running about but with poor muscle coordination Ate food later in the day

Complete and lasting recovery

EXPERIMENT 4—Monkey, weight, 42 Kg

10 31 a m Injected subcutaneously 80 mg of cocaine hydrochloride per kilogram of body weight

10 36 a m Animal had violent clonic convulsions

10 38 a m Injection of barbitol paraldehyde solution in same dosage as in Experiments 1 and 3, intravenously Immediate cessation of convulsions, sound sleep

12 46 p m Beginning to waken

3 20 p m Animal was rather unsteady on his feet but ate a banana

Permanent and complete recovery

EXPERIMENT 5—Monkey, weight, 29 Kg

9 30 a m Injected 40 mg of cocaine hydrochloride per kilogram, subcutaneously

9 39 a m Animal had severe clonic convulsions No treatment was given Animal had convulsions with intervals of relative quiet during which periods the respiratory movements became more rapid and shallow

9 55 a m Animal died

EXPERIMENT 6—Monkey, weight, 36 Kg

10 36 a m Injected subcutaneously 100 mg of cocaine hydrochloride per kilogram

10 40 a m Animal had violent clonic convulsions

10 41-43 Intravenous injection of the same dosage of barbital sodium and paraldehyde as in Experiments 1, 3 and 4 Immediate cessation of convulsions, deep sleep

1 21 p m Began to waken

1 40 p m Animal raised his head and looked about

2 04 p m Animal was replaced in his cage

Complete recovery in a few hours

EXPERIMENT 7—Monkey, weight, 22 Kg

10 52 a m Injected subcutaneously 30 mg of cocaine hydrochloride per kilogram

11 20 a m Animal had violent convulsions

11 44 a m Animal died by respiratory failure

EXPERIMENT 8—Same animal as used for Experiment 4 one month later, weight, 46 Kg

9 30 a m Injected 20 mg of cocaine hydrochloride per kilogram, subcutaneously

9 42 a m Animal was wild and delirious No signs of convulsions at any time Recovery uneventful

Condensation of Results

Animal	Cocaine Hydrochloride, Mg per kg	Treatment		Results
		Barbital Sodium, Mg per kg	Saturated Solution of Paraldehyde Cc per Kg	
8	20			Recovery
5	40			Death
7	30			Death
1	40	70	3.5	Recovery
2	60	35.6	1.75	Death
3	60	70	3.5	Recovery
4	80	70	3.5	Recovery
6	100	70	3.5	Recovery

It is evident from a study of the accompanying table that the minimal lethal dose of cocaine hydrochloride administered subcutaneously to the rhesus monkey is approximately 30 mg per kilogram of body weight. How much less would have been fatal we do not know but we believe that for purposes of calculation the minimal lethal dose is safely considered to be below 30 mg per kilogram.

Since animal 6, receiving 100 mg of cocaine hydrochloride per kilogram, recovered on treatment, we believe the upper limit had not been reached. However, on the basis of 100 mg per kilogram being a dose from which recovery is safely obtained, we are justified in saying that the minimal lethal dosage *with* treatment after convulsions

are well established is well over three times the minimal lethal dose in the untreated animals

Animal 2 well illustrates a point emphasized in our earlier paper, namely, that it is absolutely necessary to give enough of the hypnotics to prevent all evidences of cortical stimulation. The dosage of the barbitol paraldehyde mixture was in this instance too small because muscle twitchings and mild tremors developed some time after the antidote had been administered. The death of this animal we attribute largely to incomplete control of the cortical stimulant action of cocaine affecting in a harmful manner the injured respiratory center. We fully realize, however, the possibility of the hypnotics antidoting the actions of cocaine on the midbrain or the medulla as well as on the cortex.

Hofvendahl² in 1922 reported a single experiment on the monkey poisoned by 80 mg of cocaine hydrochloride per kilogram of body weight, then treated by use of a barbituric acid derivative. The animal recovered. A month later the same animal was killed by 40 mg of cocaine hydrochloride per kilogram. This experiment by Hofvendahl together with our eight experiments supported by the foundations laid in our experiments on rabbits and dogs, we believe fully justify our conclusions.

Artificial respiration alone is quite satisfactory in the treatment of cocaine poisoning in the rabbit but quite futile in the dog and evidently also in the monkey (animal 2). Hypnotic drug treatment of the poisoning was, on the contrary, progressively more successful in the higher mammals, dog and monkey. These facts we believe indicate a progressively increasing controlling influence on the higher centers of the brain on the medullary centers with the increasing complexity of the brain.

Since the experiments on the dog were more favorable than on the rabbit and the experiments on the monkey, in turn, were more favorable than those on the dog, it follows that acute cocaine poisoning in man should be correspondingly more effectively treated by the same general method.

SUMMARY

1. Acute cocaine poisoning in the rabbit, dog and monkey has been proved to be readily and satisfactorily treated by appropriate hypnotics (barbitol sodium with paraldehyde³) administered intravenously.

2. Hofvendahl, A. *Ztschr f Hals-, Nasen- u Ohrenh* 1 233, 1922.

3. It may be of interest to note that solutions of barbitol sodium and paraldehyde are quite stable, hence they may be prepared as stock solutions for use in emergencies.

2 A proper dosage of the hypnotic, given intravenously, causes immediate cessation of cocaine convulsions in the monkey, dog and rabbit, and maintains depression for a time sufficient to allow more or less complete detoxication of cocaine to occur

3 Manifestations of cortical stimulation must be absolutely controlled by a proper dose of the hypnotics, otherwise, the cerebral stimulus from cocaine so affects the cocaine poisoned medullary centers as to lead to their complete failure

4 The higher the type of animal employed the greater is the difference between the minimal lethal dose in the untreated animal and the dose recovered from when treated by the hypnotic drug method

5 We believe that man, being of a still higher order, would therefore be still more subject to successful treatment of acute cocaine poisoning by the use of the proper hypnotics

CORRECTION

STENOSIS OF THE ISTHMUS (COARCTATION) OF THE AORTA AND ITS DIAGNOSIS DURING LIFE

JOHN T KING, JR., M D

In the third paragraph of this article, published in the July issue of the ARCHIVES OF INTERNAL MEDICINE, an error was made in referring to the cases analyzed by Dr Abbott in 1915. The number should have read 212, instead of twelve.

Book Reviews

DISEASES OF THE HEART By DR HENRI VAQUEZ, Professor of the Faculty of Medicine of Paris, Physician to L'hospital de la Pitie, Member of the Academy of Medicine (Paris) Translated and edited by GEORGE F LAIDLAW, MD, Associate Physician to the Fifth Avenue Hospital, New York City, Fellow of the Academy of Medicine of New York Introduction by WILLIAM S THAYER, MD, FRCPI (Hon) Professor Emeritus of Medicine, Johns Hopkins University, Visiting Physician to the Johns Hopkins Hospital, Baltimore, Associate Foreign Member of the Academy of Medicine (Paris) Pp 743 Philadelphia W B Saunders Company, 1925

This work is a rather thorough exposition of diseases of the heart and consists largely of the personal views of the author

The points of especial excellence are the vivid clinical pictures that the author portrays, the section on congenital heart disease, and the discussion of the arrhythmias Also, in the discussion of electrocardiography the author has succeeded in keeping on safe middle ground, avoiding the Scylla of over-optimism and the equally undesirable Charybdis of total disappointment

The portion of the book dealing with endocarditis shows a wide divergence of opinion from that entertained today by most British and American cardiologists The total disregard of the later reports on rheumatic heart disease and streptococcus endocarditis shows that the author has failed to be convinced by these reports

Some of his statements are surely open to question It is doubtful if simple benign endocarditis and infectious endocarditis may be as sharply differentiated as he does it Surely in those cases in which the streptococcus is recovered from the blood the prognosis is not as bad as he pictures it, nor are the organisms as difficult to recover as he would lead us to believe He confesses the inadequacy of drug therapy, but does sufficiently stress the most valuable therapeutic agent at our command namely, rest in bed

The same difference of opinion is exhibited in dealing with valvular disease One is left under the impression that if the valves are once damaged, the failure of the heart must be progressive This question has not yet been satisfactorily answered Certainly, the effect of active infection and recurrent infection has not been sufficiently emphasized by the author and many cardiologists will state that in the absence of infection the damaged heart will deteriorate no more rapidly than the undamaged heart

In that portion of the book devoted to angina pectoris, the sharp differentiation between angina pectoris of effort and that of decubitus is somewhat questionable The case in which the anginal attack appeared coincidently with a demonstrable dilatation of the heart is an exceedingly interesting one, if the observation is accurate Mention of the purin base diuretics in angina or the employment of surgical procedure for the relief of pain is lacking

Advocacy of vigorous arsenical therapy in the treatment of cardiovascular syphilis will not meet with universal approbation Rather convincing proof has been offered to support the view that such procedure is not without very real danger

In the consideration of the cardiac arrhythmias sinus irregularity has been relabeled the youthful type of arrhythmia It is of course, common enough in all ages and its incidence in old age is but little exceeded by that in youth

A discussion of quinidine occupies most of the treatment of auricular fibrillation Digitalis is mentioned only as a preliminary measure to restore normal rhythm A therapeutic measure as efficient as digitalis in the treatment of

auricular fibrillation should be given more consideration in a discussion of the treatment of this condition. The statement that "quinidine may be given with advantage to all patients suffering from complete arrhythmia" should not go unchallenged even though the author qualifies this by later presenting a list of contraindications. The existence of active endocarditis is such an absolute contraindication that the original statement should never appear without immediate qualification.

The book as a whole exhibits the enormous extent of the author's work and, in most instances, the accuracy of his observation. It is the result of painstaking effort and the minutest attention to detail. No subject escapes the closest scrutiny. The value of the book is further enhanced by an excellent bibliography. It provides a valuable addition to any library on diseases of the heart.

Lastly, the translator should be highly commended for his work in preserving the vividness of the clinical portrayals.

PHYSICAL DIAGNOSIS OF DISEASES OF THE CHEST By PRATT and BUSHNELL
Price, \$7.50 Philadelphia W B Saunders Company

This book was written as the result of experiences in teaching physical diagnosis to medical officers of the Reserve Corps in the late war. That work demonstrated that many physicians were lamentably unskilled in methods of examination and in interpretation of examinations, and the writers of this volume begin with fundamentals—physical laws of sound formation and transmission—apply these to normal cases and later compare the deviations from normal with their causes and interpretations.

Palpation, percussion, auscultation, resonance and fremitus are considered first in normal, later in pathologic cases, with separate chapters devoted to diseases of the lungs and pleura and a special chapter on pulmonary tuberculosis.

The physiology and anatomy, normal and abnormal, of the heart are considered, next, general procedures of diagnosis, inspection, palpation, percussion and auscultation of the heart, with discussion of normal and abnormal observations as well as of information to be gained from the condition of the blood vessels. A chapter on instrumental methods of diagnosis includes use and interpretation of blood pressure examinations, venous pressure, the sphygmogram, phlebogram, electrocardiogram, orthodiagram and teloradiogram.

The cardiac irregularities, valvular disease and myocarditis are carefully considered, as well as pericardial and aortic disease. Especially instructive is the chapter on cardiac neuroses, though short, it gives valuable help in their detection.

The cardiac portion of the book is commendable as any well written treatise on the subject is, but the section on pleural and pulmonary diagnosis is especially well done and deserves widespread study on the part of the general clinician.

MEDICAL DIAGNOSIS By JAMES M. ANDERS and LEONARD NAPOLEON BOSTON
Price, \$12 Philadelphia W B Saunders Company

This is the third edition. It retains the general plan of the widely used second edition but is entirely reset and brought up to date with reference to newly described diseases and methods. Description of cases has been omitted to give space to a more comprehensive discussion of diagnosis.

The volume emphasizes throughout with diagnostic and differential tables the features of the condition discussed both clinical and laboratory. The correlation between clinical manifestations and the structural changes as well as special etiologic factors of infection, are also discussed.

The volume is a well conceived, carefully executed text containing in not too brief form all that can be included in any single book.

INVESTIGATIONS INTO THE MORPHOLOGY OF THE RAY FUNGI By J ORSKOV, the State Serum Institute, Copenhagen Pp 171 Copenhagen Levin and Munksgaard, 1923

This monograph is a cultural and morphologic study of certain of the ray fungi These are compared with the corynebacteria and mycobacteria Certain criteria are given for a new classification and nomenclature of the fungi The close resemblance of certain corynebacteria and mycobacteria to the fungi is considered The monograph is of use chiefly to bacteriologists as a reference

STUDIES OF GONOCOCCUS TYPES AND GONOCOCCUS IMMUNE SERUMS By ERIK VOLLMOND Pp 187 Copenhagen Levin and Munksgaard, 1923

Because of divergent results obtained with the complement fixation test in gonorrhea regardless of the clinical course of the infection, Erik Vollmond, in consideration of these results, presumed that the gonococcus, like the meningococcus and other bacterial species constitute a heterogeneous family, comprising types with different antigenic properties He believes, as the result of serologic studies, that most gonococcus strains can be arranged in three types (I, II and III) The type I infection is less severe than the other two

CLASSIFICATION OF THE STRAINS BELONGING TO THE TYPHOID-PARATYPHOID GROUP OF BACTERIA TOGETHER WITH A DEMONSTRATION OF DIFFERENCES IN AVIDITY By A HECHT-JOHANSEN Pp 207 Copenhagen Levin and Munksgaard, 1923

The first part of this monograph is a serologic study of approximately 100 strains of the typhoid-paratyphoid-enteritides group of bacteria in an attempt at classification On the basis of results obtained the author divides these strains of bacteria into eleven groups, some large, others small The second part is a study in avidity and the author finds a marked inequality with which bacterial strains bind immune substance The chief value of this monograph is as a reference for bacteriologists or immunologists interested in these problems

STUDIES ON THE PAPILLAE VALLATAE OF MAN By DR AUGUST JURISCH Pp 157 Munich J F Bergmann Berlin Julius Springer, 1922

This is a comprehensive historical review and histologic study of the papillae vallatae of the human tongue Its chief value is to anatomists and histologists There are numerous tables, charts, drawings and photographs One chapter concerns the foramen caecum and the sulcus terminalis

FOOD FOR THE DIABETIC By MARY PASCOE HUSSEYSON New York MacMillan Company

The first edition of this little volume filled a definite need and ranked among the best of the many little books on diabetes The slight revisions of the second edition make this new printing more valuable

GLANDULAR FEVER (INFECTIOUS MONONUCLEOSIS) [†]

C W BALDRIDGE, M D

F J ROHNER, M D

AND

G H HANSMANN, M D

IOWA CITY

Since Filatow's ¹ first allusion in 1885 to an idiopathic lymph adenopathy there have been more than 110 articles published on glandular fever, and about half as many articles on similar or identical conditions variously named. In the eighteen nineties numerous small epidemics were reported in England, on the Continent, and in this country. In 1907 Turk ² reported blood observations in cases with lymphadenopathy, and since 1920 there has been a generalized feeling that mononucleosis is a constant feature of glandular fever.

Even now, forty-one years after the first recorded observations on the disease, there is considerable confusion, and some able clinicians are inclined to disregard the whole group of cases rather than draw definite conclusions as to the existence of a true disease entity among them. Until recently most important textbooks and systems of medicine contained at most only brief mention of the condition. The clinical features of glandular fever, including its epidemiology, symptomatology, physical observations and course, are abundantly described in the literature. The pathology has not been sufficiently studied and the etiologic agent has not been determined. The occurrence of a very peculiar and interesting blood picture in glandular fever seems to be largely responsible for the renewed interest in the condition and has made the diagnosis possible in many sporadic cases.

It is our purpose to review the established observations to determine, if possible, the true significance of the occurrence of abnormal lymphocytes in the blood stream, and to add our clinical, pathologic, bacteriologic and experimental findings in glandular fever to the existing knowledge of this condition.

[†]From the departments of internal medicine and pathology, State University of Iowa College of Medicine.

1 Filatow, N. Lectures on the Acute Infectious Diseases of Children, 1885.

2 Turk, W. M. Septische Erkrankungen bei Verkümmerng des Granulozytensystems, Wien klin Wchnschr 20 157, 1907.

CLINICAL DATA

The present study is based on observations in fifty cases, thirty-six of which are taken from the house records of the University Hospital, and fourteen from the outpatient department and private files. We shall also consider blood studies and other data obtained by a survey of junior medical students during the recent epidemic.

Our first case was seen in 1914. Because of fever and an enlarged spleen, typhoid fever and tuberculosis were carefully ruled out and a diagnosis of "febricula" was finally arrived at by exclusion. A similar case was seen in 1917. In 1918 and 1920 two cases were seen which because of the especially marked mononucleosis were termed "acute sublymphatic lymphocytosis" according to the suggestion of Turk.² In 1922 and 1923 several cases were called "infectious mononucleosis"

TABLE 1—*General Observations in Series*

Symptoms	Percentage	Physical Observations	Percentage
Headache	70	Fever	100
General malaise	70	Enlarged glands	100
Sore throat	68	Postcervical	88
Tender glands	60	Axillary	86
Backache	54	Subangular	64
Chilliness	44	Submaxillary	52
Anorexia	38	Inguinal	50
Coryza	36	Epitrochlear	32
Sweating	34	Submental	10
Weakness	32	Tender glands	76
Cough	30	Throat injected	58
Dizziness	26	Enlarged spleen	48
Sore bleeding gums	26	Enlarged tonsils	44
Nausea	24	Tonsils removed	32
Stiff neck	24	Membranous angina	22
Abdominal pain	16	Enlarged liver	16
Vomiting	12	Peritonsillar abscess	12
Photophobia	10	Enlarged thyroid	4
Aplthous sore mouth	10	Tenderness in abdomen	4
Pleurisy	8		
Nervousness	8		
Loss of weight	6		
Fainting	6		
Constipation	4		
Diarrhea	2		

because of their similarity to patients reported by Longscope³ and others. A recognized epidemic did not begin until December, 1924, and its height was reached in March, 1925. Thirty-two of our fifty cases were seen during the first six months of 1925.

Thirty-four of the cases were university students, six were nurses, six were patients receiving antisyphilitic treatment, two were physicians and two were school children referred from the surrounding territory. The youngest was a boy of 6½ years, the oldest a man of 40. The age incidence was markedly influenced by the fact that all patients under 14 years of age were examined in the department of pediatrics and so do not appear in this report. The foregoing exception was the son of a physician who was seen privately by one of us. The average age was

3 Longscope, W. T. Infectious Mononucleosis (Glandular Fever), with a Report of Ten Cases, *Am. J. M. Sc.* 164:781 (Dec.) 1922.

231 years Thirty-eight of our patients were males and twelve were females

The more common symptoms and physical observations met with in our series are given in table 1

The heart, lungs and gastro-intestinal tract were essentially normal in all cases In a few instances a systolic murmur was heard at the pulmonary area during the febrile period and transient signs of moisture at the bases of the lungs were occasionally encountered Roentgen-ray or fluoroscopic examination of the chest was done in nine of the cases, but none showed mediastinal shadows or other important lesions All of the thirty-six patients admitted to the hospital had fever The highest temperature recorded was 105.2 F Four cases had maximum temperatures of 104 F or above, seven were between 103 and 104 F, nine between 102 and 103 F, six between 101 and 102 F, two between 100 and 101 F and seven between 99 and 100 F

The relation between the pulse and the temperature was the same as is seen in other acute infections

LABORATORY DATA

A transient slight albuminuria was found in 42 per cent, and 32 per cent showed occasional pus cells Hyaline casts were seen in a few instances, while one patient developed a definite hemorrhagic nephritis The Wassermann reaction was done in sixteen cases and was found to be positive in six All six of these patients developed glandular fever while under active antisyphilitic treatment Cultures for diphtheria bacilli were done in seventeen cases and six were reported suspicious, but in no instance was a virulent organism isolated Widal reactions with both typhoid and paratyphoid organisms were done in four cases and were found negative Of the six in which tuberculin skin tests were done, five reactions were interpreted as negative and one as moderately positive Blood cultures were done in eight instances with seven negative results In one a diphtheroid bacillus grew in both bouillon and blood agar plates The sputum in the few cases in which it was present was consistently negative for tubercle bacilli Twenty-one of the cases were not examined for Vincent's organisms Of the remaining twenty-nine in which smears were made, twenty-seven were found to have large numbers of both the spirochetes and fusiform bacilli Smears were taken directly from the membranes in seven of the eleven cases in which membranous angina was present and were positive in all instances In the other four cases smears were not made The blood observations were variable A leukocytosis of varying degree was present in most of the cases, sometime during the course In general, cases with marked temperature reactions showed a leukocytosis with relative polymorpho-nuclear increase during the febrile period The highest percentage of

cells of myelocytic origin encountered was 87, while the highest percentage of mononuclear cells found was 99. The highest total leukocyte count was 26,950. Most of the cases which were carefully followed developed a leukopenia sometime during their course, usually in from two to four weeks after the onset. The lowest leukocytic count in the series was 3,400.

It should be stated in the beginning that any attempt to be exact in the classification of the mononuclear cells seen in these cases is a very presumptuous task. We are inclined to follow the example of Longcope who classifies them as abnormal mononuclears. Normal lymphocytes and almost all conceivable varieties of abnormal lymphoid cells are present. Many of the cells are so atypical as to make their origin very questionable and require special stains to determine whether they are of endothelial or lymphoid nature. Most of the blood counts presented here are taken from the case records and are the results obtained in the course of routine study by interns. Doubtful and unusual cases were more carefully studied.

The average of 136 counts on the fifty patients is as follows: Erythrocytes, 4,800,000, hemoglobin, 92.2 per cent, leukocytes, 10,177, polymorphonuclear neutrophils, 48.4 per cent, mononuclear cells, 50.2 per cent, eosinophils, 1.1 per cent, basophils, 0.2 per cent.

Blood counts and smears for organisms of Vincent's angina were done on sixty-seven junior medical students during the height of the epidemic in March, 1925. Of these, twelve developed definite symptoms of the disease in question and are included in the foregoing group of fifty cases. The onset of the illness in each of the twelve cases was rather insidious, and most of the men continued to go to classes and mingled freely with their fellow students, since segregation seemed quite impracticable. The remaining fifty-five did not consider themselves sick enough to report to the dispensary in spite of the fact that they were about the hospital most of the time.

The average of the blood counts in these fifty-five students is as follows: erythrocytes, 5,050,000, leukocytes, 8,185, polymorphonuclear neutrophils, 54.5 per cent, normal appearing lymphocytes, 14.5 per cent, abnormal mononuclears, many of which approach the normal monocyte in appearance, 29 per cent, eosinophils, 1.7 per cent, basophils, 0.2 per cent. The highest percentage of abnormal mononuclears seen in this series was 57, while the lowest was 3. The highest leukocyte count was 14,500, the lowest, 4,100.

Smears from the gum margins, stained with carbolfuchsin gave the following results. Forty-seven were markedly positive for organisms of Vincent's angina containing both spirochetes and fusiform bacilli in large numbers, three contained but few organisms and five were negative. In no case was there marked inflammation of the gum margins nor membranous angina.

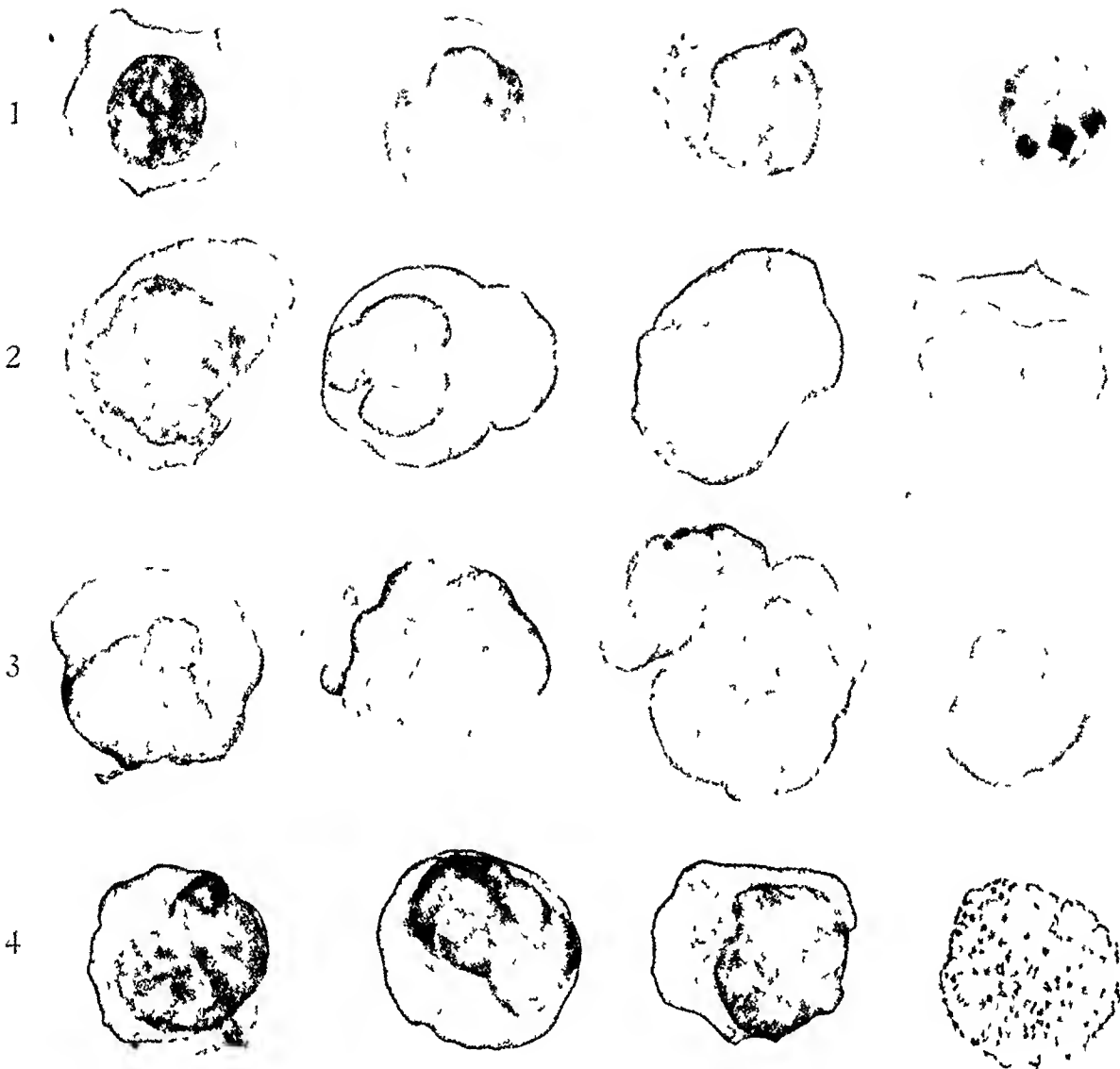


Fig 1—Only a few varieties of abnormal cells are illustrated and an attempt has been made to place morphologically related cells in the same row. Average cell types rather than the most bizarre have been chosen. The cells have been drawn to scale and the nucleus of the first cell in row 1 represents the size of an average red corpuscle.

Row 1. The first three cells in this row are intermediate lymphocytes with only minor variations from the normal. Small vacuoles in the cytoplasm will be noted in the first two. The fourth cell in this row shows condensation of chromatin at the periphery of the nucleus with a suggestive clock-face appearance. This type of cell made up 99 per cent of the circulating leukocytes in one case.

Row 2. These cell types occur in small percentages in many of the cases. Their very close approach to ordinary granular monocytes is readily seen.

Row 3. This general type of cell, which in appearance closely approaches the hyaline cell or the "vascular endothelial cell" of McJunkin, often makes up 75 per cent of the circulating leukocytes in cases of glandular fever. We have no explanation for the small nuclear protrusions but we do not feel that they are artefacts. Apparently multinucleated elements such as the third cell in this row are not especially common, and none of them present an arrangement suggestive of a recent mitosis.

Row 4. These large cells with wavy inner nuclear structure and deeply basophilic, occasionally vacuolated cytoplasm seem no doubt lymphocytic. They do not form a high percentage of the total leukocytes. The cell with the basophilic granules is of rather frequent occurrence in glandular fever. Such cells are larger and the granules are smaller and more numerous than those of the ordinary mast cell.

Occasionally all of these cell types are found in the same patient. The type illustrated in row 3 is the most frequent and when such cells occur, they are usually present in large numbers to the almost complete exclusion of all other types. The cell types in row 1 often occur in high percentages but are usually associated with a few cells such as are seen in rows 2 and 4. The same type of abnormal cell usually persists throughout the course of the disease. This is especially true of those in row 3.

On direct questioning thirty-eight of the fifty-five admitted that they had two or more of the symptoms listed above, though they were in no instance severe. Also nineteen reported recently enlarged superficial glands, principally in the cervical region.

All of these students were in good health six months after this study. A few contrasting types of cases may be briefly cited.

REPORT OF CASES

CASE 1—A. A., an unmarried woman, aged 22, stated that the onset was gradual with malaise and dull pain in the neck for one week before admission. A tooth was extracted before admission without relief. The throat was slightly sore. The tonsils were enlarged and red. There was general glandular enlargement especially of the cervicals, which were tender. The spleen was 8 cm. below the costal margin. Convalescence was much protracted, with enlargement of the thyroid gland and mild hyperthyroidism. The spleen was still palpable after seven years.

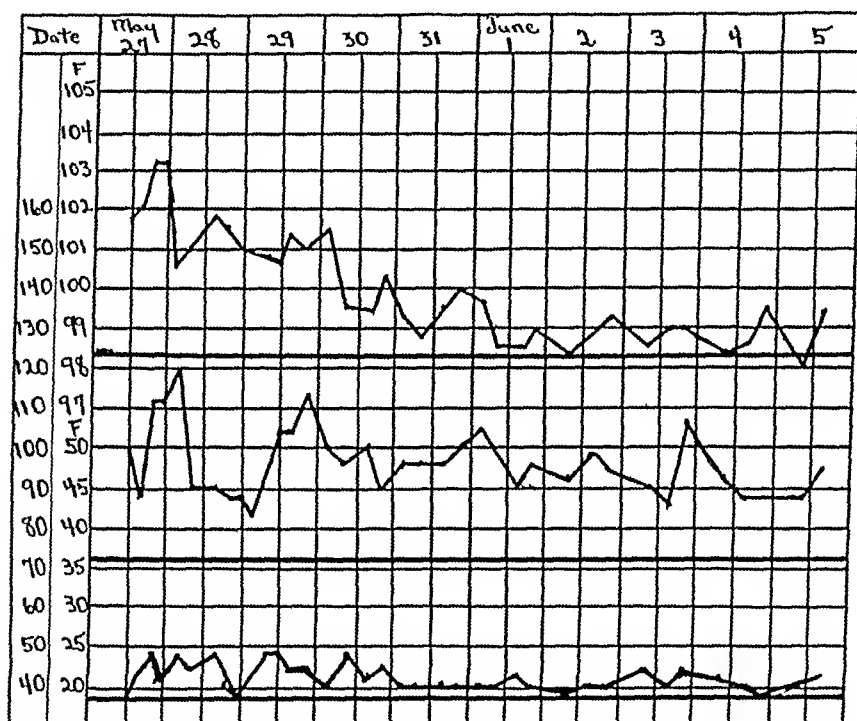


Fig. 2 (case 1)—Temperature, pulse and respirations. This patient had an irregular fever for a week prior to admission.

TABLE 2—Case 1

Date	Red Blood Cells	Hemo-globin, per Cent	White Blood Cells	Polymor-phonuclear Neutrophils	Mononu-clears*	Eosino-phils	Baso-phils
5/26/18			16,000				
5/27/18	4,430,000	98	14,200	15	85		
5/28/18	4,230,000	96	12,800	16	84		
5/30/18			10,600	18	82		
6/ 2/18			6,000	18	82		
6/ 8/18			4,000	37	65		
6/10/18			3,400	32	68		
6/11/18	1,280,000	95	3,600	36	61		
6/18/18			4,000	16	52	2	
6/25/18			5,800	60	38		2
6/31/18			13,400	41	59		
9/ 5/25			7,800	54	41	3	2

* Most of the mononuclear cells were rather large and had irregular nuclei. On one occasion two nucleated red cells and some stippled cells were seen.

CASE 2—J P J, a man, aged 25, had a slight cough for two weeks before the onset, which was rather sudden with abdominal cramps, vomiting and profuse sweating. Prostration was not marked during the period of septic temperature. The left cervical and right axillary glands were 1.5 cm in diameter. The spleen was not felt. Convalescence was protracted.

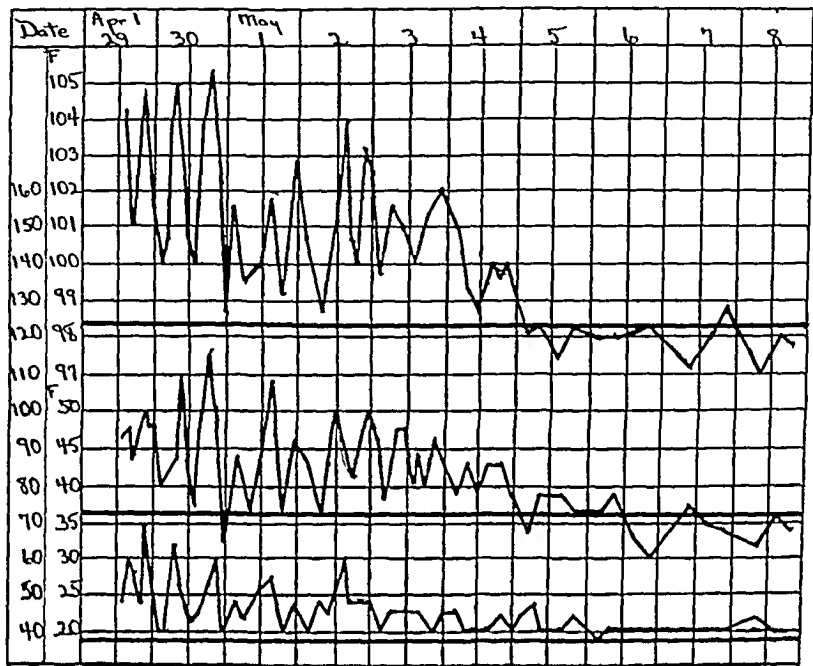


Fig 3 (case 2) —Marked septic type of temperature in patient admitted on second day of illness

TABLE 3—Case 2

Date	Red Blood Cells	Hemoglobin, per Cent	White Blood Cells	Polymorpho nuclear Neutrophils	Mono nuclears
4/28/24			20,000		
4/29/24	4,840,000	98	15,150	69	31
4/30/24			12,800		
5/ 4/24			8,100		
5/15/24	3,820,000	75	12,500	40	60
6/ 4/24	4,160,000		8,500	43	57
12/21/24			8,800	72	28
3/ 5/25	4,770,000	93	8,000	52	48

Blood smears contained very few normal appearing lymphocytes

CASE 3—E N, an unmarried woman, aged 19, had a rather abrupt onset. She was one of three patients admitted the same day. Sore throat, tender glands in the neck, chills, headache, backache, nausea, and general malaise were noted.

The cervical glands were markedly enlarged, the other lymph glands were not remarkable. The spleen was not felt. A blood culture was sterile. She was hospitalized for thirty-one days, convalescence was protracted.

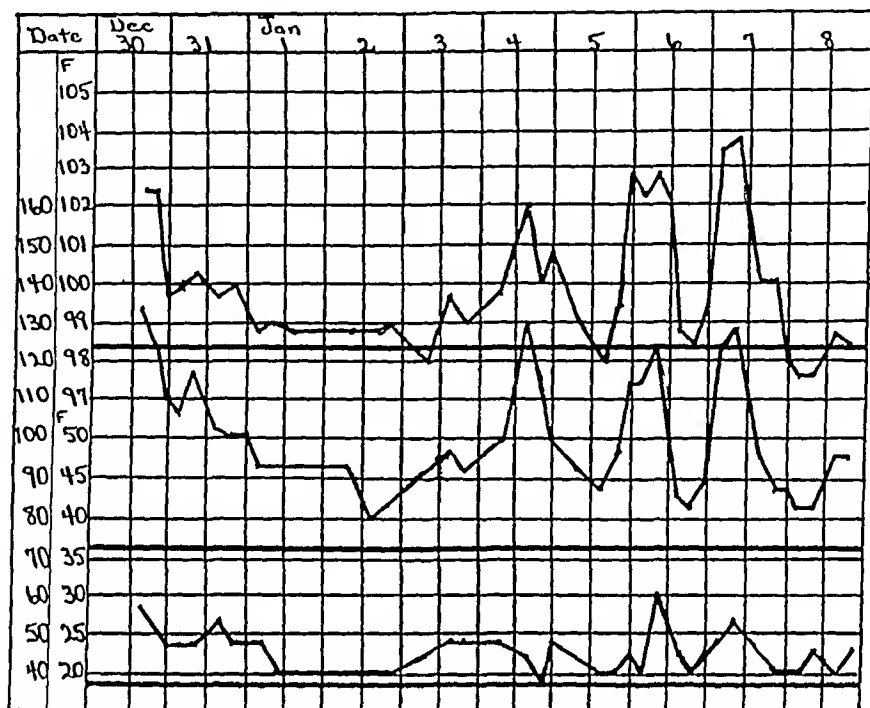


Fig. 4 (case 3) —One of several recurrent febrile attacks occurring in this case. The cervical glands reenlarged and became acutely tender and painful with each recurrence of the fever.

TABLE 4—Case 3

Date	Red Blood Cells	Hemo- globin, per Cent	White Blood Cells	Polymor- phonuclear Neutrophils	Mononu- clears*	Eosino- phils	Baso- phils
12/31/24			17,000	70	30		
1/ 1/25				63	36	1	
1/ 2/25			11,400	75	24	1	
1/ 4/25			11,100				
1/ 6/25			15,000	85	13	2	
1/ 7/25			11,100	73	26	1	
1/13/25			6,400	73	25	2	
1/16/25			8,400	51	45	2	2
1/26/25	3,950,000	75	7,700	37	60	3	
10/23/25	4,320,000	76	7,550	41	56	3	

* Nearly all of the mononuclear cells were abnormal.

CASE 4—K. K., a man, aged 26, stated that the onset was insidious with headache, malaise and anorexia. The tonsils were enlarged with a small membrane containing organisms of Vincent's angina on the left. There was moderate general glandular enlargement. The spleen was not felt. The urine contained blood and a few casts for six months. Convalescence was protracted, recovery was complete.

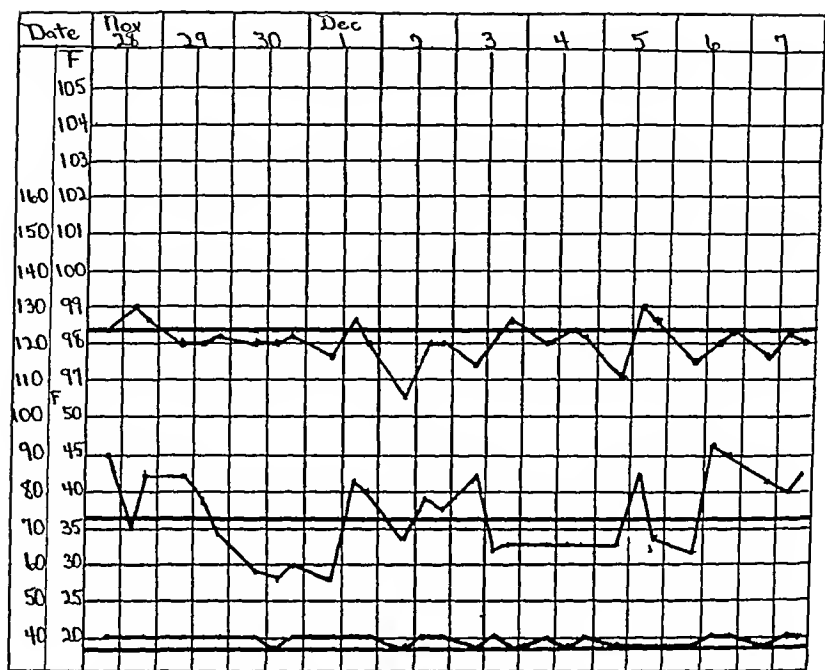


Fig 5 (case 4) —Almost complete absence of fever with marked mononucleosis. There was no history of acute onset or marked febrile reaction prior to admission.

TABLE 5—Case 4

Date	Red Blood Cells	Hemo globin, per Cent	White Blood Cells	Polymorpho nuclear Neutrophils	Mono- nuclears*	Eosino phils
11/27/22			20,000			
11/28/22	1,830,000	97	21,250	9	90	1
11/29/22			20,500	9	91	
11/30/22			26,950	15	85	
12/ 1/22			25,200	13	86	1
12/ 2/22			14,700	11	88	1
12/ 4/22			12,400	14	86	
12/ 6/22			10,500	56	44	
12/ 8/22			8,250	41	59	
12/11/22			7,100			
12/14/22			6,500	32	63	5
12/18/22			6,700			
12/26/22			6,300	44	56	
1/ 6/23	4,370,000	89	7,200	59	40	1

* Many of the mononuclear cells were large with irregular lobulated nuclei

REACTION OF LEUKOBLASTIC TISSUE TO FOREIGN PROTEIN

Four of our patients were given 25,000,000 killed typhoid bacilli intravenously during the course of their illness. The blood report during the subsequent reactions is recorded in table 6. The averages are in absolute numbers and percentages were obtained by counting 200 cells. The temperature reactions were all very similar.

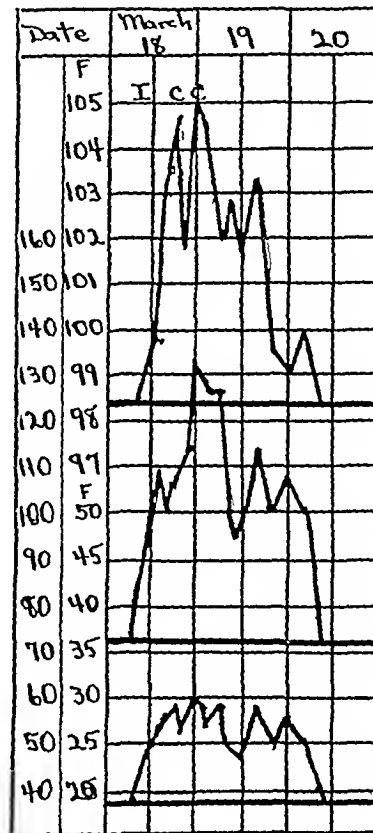


Fig 6—The febrile reaction following inoculation of 25,000,000 killed typhoid bacilli, this was more prolonged and irregular than is usually seen and was associated with marked constitutional symptoms

TABLE 6—Average Blood Observations in Absolute Numbers Per Cubic Millimeter After Intravenous Injection of Killed Typhoid Bacilli in Four Cases

	Leuko cytes	Poly morpho nuclears	Normal Lympho- cytes	Abnormal Mono- nuclears	Eosino- phils and Basophils
Before vaccine	6,375	3,350	1,585	1,403	37
3 hours after vaccine	13,000	11,390	1,054	1,356	100
7 hours after vaccine	9,338	7,035	912	1,326	15
24 hours after vaccine	7,075	3,536	1,397	1,997	145

BACTERIOLOGY

The six glands removed were each divided under aseptic conditions and half was used for histologic study and the other half for bacteriologic examination. Cultures were made in veal bouillon, on plain agar and on blood agar. Diphtheroid bacilli were obtained from four of the six glands. In three instances the cultures were pure. In one there was also *Staphylococcus albus*, which later overgrew the medium to such an extent that we did not isolate the diphtheroid from this case in pure culture. Of the remaining two glands, the cultures in one remained sterile and in the other a very small, rapidly growing avirulent coccus was obtained. Initial growth of the diphtheroid bacilli occurred only in the veal bouillon.

Our efforts were focused particularly on the three diphtheroid organisms obtained in pure cultures. Studies were made by two groups of observers independently and the results correlated. Initial cultures grew very slowly requiring from five to seven days for clouding of the mediums. Subcultures grew somewhat more rapidly. The organisms also grew in subculture on serum-glucose-meat-infusion-agar and on Dorset's egg medium.

The organisms isolated from two of the cases were alike morphologically, in staining characteristics and in the fermentation of various sugars. These organisms were short, slender rods with beaded ends and were often slightly curved. They stained poorly with methylene blue and were gram-positive. They produced neither acid nor gas in dextrose, lactose, saccharose, maltose, mannite, salicine, dulcitol or raffinose. The third organism differed somewhat in morphology, cultural characteristics and in the fermentation of sugars. This organism was longer, thicker and more curved than the foregoing, and after numerous subcultures grew fairly well on plain agar and on blood agar. It also produced acid in dextrose, lactose, saccharose and maltose.

Gland emulsions were inoculated subcutaneously into twelve guinea-pigs with negative results. Six rabbits were given gland emulsions intravenously with negative results except for two immediate (embolic) deaths. Twelve guinea-pigs were injected either subcutaneously in the groin or intraperitoneally with veal bouillon cultures of the organisms. A fever of from 1 to 3 degrees lasting from four to five days resulted, but there was no gross adenopathic condition and very few symptoms. Six pigs were killed and examined at necropsy ten days after inoculation, but again no gross adenopathic condition was found and the organisms were not recovered from the glands. Histologically, the regional nodes were not hyperplastic as compared with those of normal pigs of the same age.

Serums were obtained from three convalescent patients. Two of these were patients from whom glands had been removed and from which diphtheroids were cultured. Neither specific agglutinins nor precipitins for any of the three cultures of diphtheroid bacilli could be demonstrated in these serums.

Dark field studies on the tissue juices from the glands were uniformly negative for spirochetes and other motile organisms.

As has already been stated, diphtheroid bacilli were isolated from six of the seventeen cases in which throat cultures were done, as well as from one of the eight blood cultures which were taken.

In our fifty cases twenty-seven of the twenty-nine examinations for organisms of Vincent's angina were positive. Seven of these smears were taken directly from membranes in the mouth or pharynx and the remainder from the gum margins. Forty-seven positive and three

doubtful smears were found among the fifty-five medical students in whom smears were made from the gum margins. Similar smears from fifty general medical patients who had neither enlarged glands nor mononuclear increases in the blood yielded forty-one positive results.

PATHOLOGY

Axillary lymph nodes were removed from six of our patients, at intervals varying from four days to six months after the onset. All

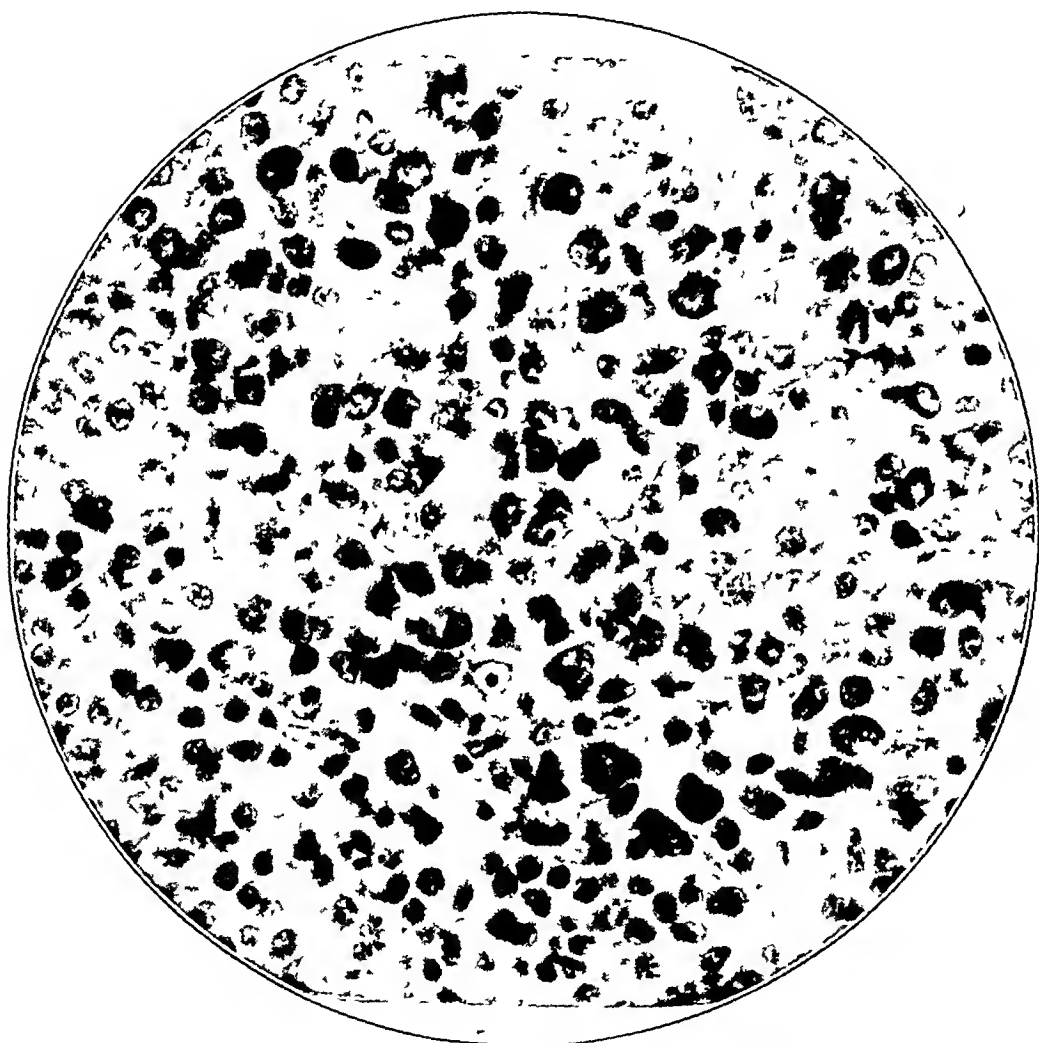


Fig. 7—Tissue showing six mitotic figures and variation in size and shape of the lymphoid cells ($\times 150$ slightly reduced)

glands were very similar both in gross and microscopic appearance. The size varied from 2 to 3 cm. in diameter and the glands were very soft and spongy. They were kidney shaped with distended white capsules and cut sections were uniformly gray and granular. Histologically, the architecture was for the most part discernible though there was much distortion by the marked lymphoid hyperplasia which compressed the sinuses and distended the capsules. Some germinal centers were replaced

by uniform lymphoid hyperplasia. Mitoses were numerous (6 per high power field) in the germinal centers and lymphatic cords, and a few were seen in the lining of the lymph sinuses. An occasional eosinophil was also seen. In all glands there was a very marked variation in the size of the lymphoid cells, many of which were found free in the lymph sinuses. Marked irregularities were common in the nuclei of the cells both in the sinuses and in the lymphatic cords. Some of these nuclei

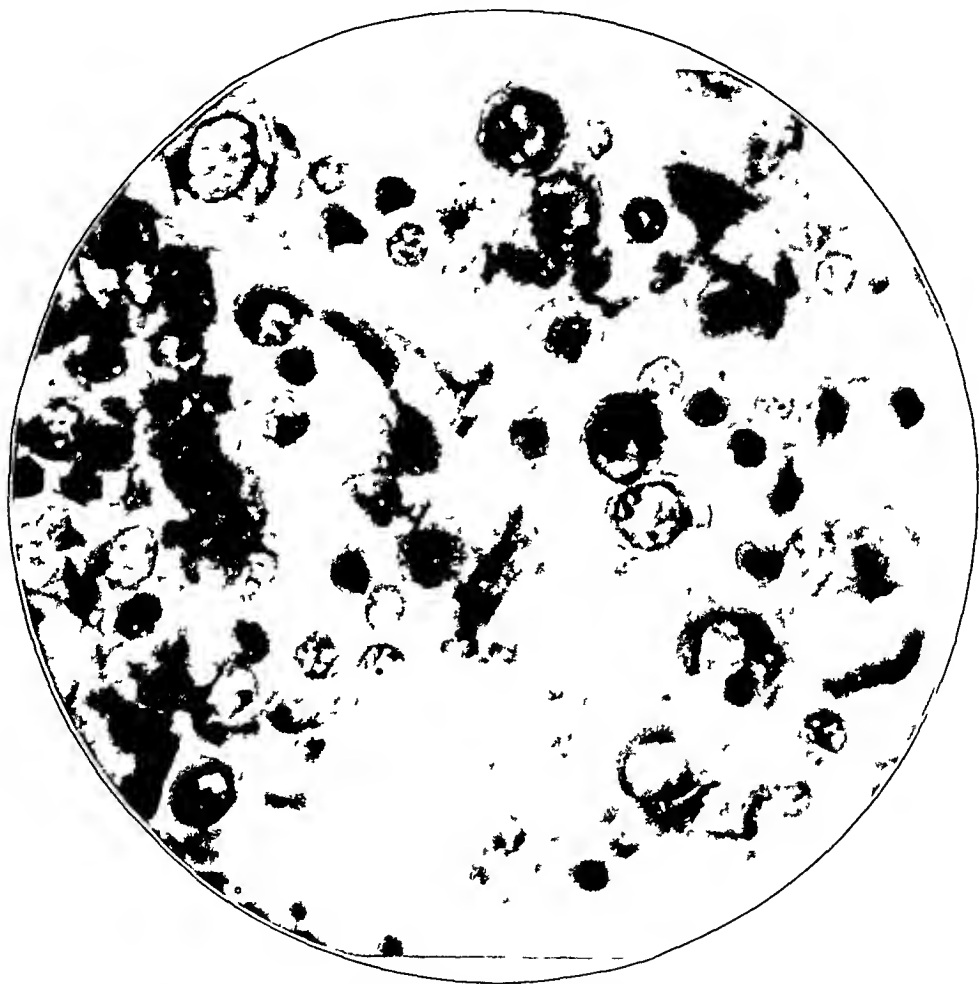


Fig 8—Tissue showing the variation in size of lymphoid cells in the lymph sinuses and the difference in the affinity of the nuclei for hematoxylin ($\times 900$ slightly reduced)

were lobulated and indented and resembled in shape the abnormal circulating elements. There was no increase in the fibrous reticulum, and no necrosis or evidence of repair in the gland which was removed six months after the initial attack of glandular fever.

A close resemblance, histologically, between the glands of glandular fever and those of the malignant lymphomas, especially Hodgkin's type,

has been pointed out by Sprunt and Evans⁴ and by Longcope. Collections of very small lymphocytes, a finding stressed by Downey,⁵ was not a prominent feature in the glands from our patients.

COMMENT

Etiology—The causative agent in glandular fever has not been determined, though the condition has from the first been considered an infectious disease. Jamison⁶ in a recent article states "Pfeiffer claimed

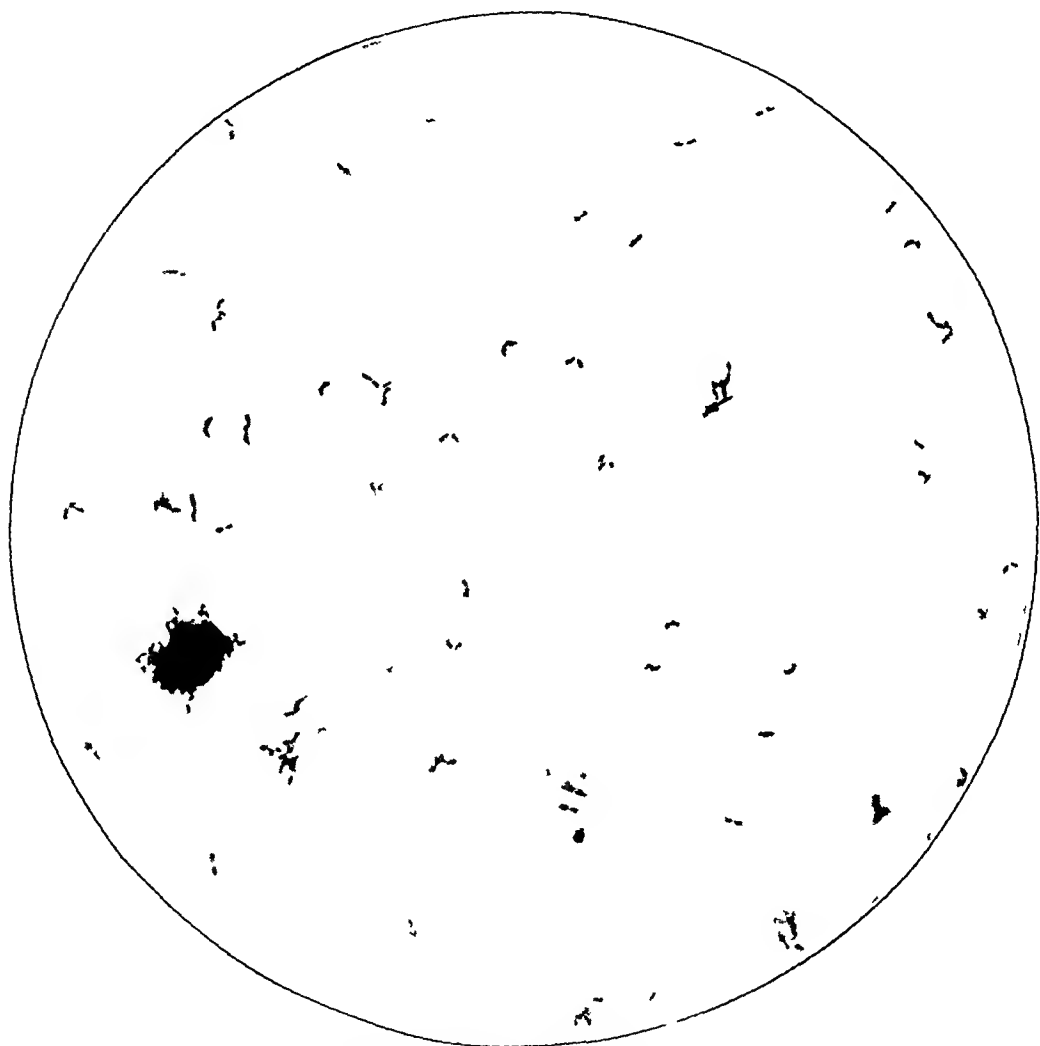


Fig 9—Diphtheroid bacilli obtained from a culture of the glands ($\times 900$ slightly reduced)

to have isolated the influenza bacillus from the glands and blood of patients suffering with this disease." We have not been able to verify

4 Sprunt, T. P., and Evans, F. A. Mononuclear Leukocytosis in Reaction to Acute Infections (Infectious Mononucleosis), *Bull. Johns Hopkins Hosp.* **31**: 410 (Nov.) 1920.

5 Downey, H., and McKinlay, C. A. Acute Lymphadenitis Compared with Acute Lymphatic Leukemia, *Arch. Int. Med.* **32**: 82 (July) 1923.

6 Jamison, C. S. Glandular Fever, *New Orleans M. & S. J.* **75**: 346, 1923.

this statement by a review of the original articles of both E Pfeiffer,⁷ who described glandular fever, and R Pfeiffer, who described *Bacillus influenzae*

Korsakoff,⁸ Lublinski,⁹ and numerous of their contemporary German clinicians were quite uniformly of the opinion that a streptococcus gaining entrance through the upper respiratory tract was the important etiologic agent in "Drusenfieber." Their reasons for such conclusions were briefly as follows: the clinical course of the disease, the appearance of the throat, the predominance of streptococci in the cultural flora of the upper respiratory tract, the occurrence, though rarely, of a rash not unlike that of scarlet fever, and the few cases in which there developed an hemorrhagic nephritis. In Neumann's¹⁰ series of thirty-seven cases, half developed suppurative adenitis and the pus contained streptococci. One case of streptococcic meningitis⁸ was met with, and in another fatal case⁸ streptococci were isolated from the enlarged cervical lymph glands at necropsy. Schleissner,¹¹ who also reported glandular fever without blood counts, found hypertrophied adenoids in all of his patients, and he felt that the adenoids were probably the portal of entry of the infectious agent. Throat cultures from his patients showed streptococci and staphylococci. Marchand¹² reported a fatal case of streptococcic septicemia with enlargement of the spleen, liver and lymph glands, in which there were 85.5 per cent lymphocytes. The total leukocyte count, however, was only 2,100. Turk² spoke of a similar case in which the superficial lymph nodes were enlarged but the liver and spleen were not palpable. The leukocyte count was only 940 and in the differential study, 532 cells were counted without a single polymorphonuclear leukocyte being seen. Some of the lymphocytic cells were atypical. A culture of the heart's blood at necropsy resulted in the growth of a single colony of *Staphylococcus aureus*. Deussing¹³ referred to a case of Ludke's in which there were 82,000 leukocytes with 85 per cent lymphocytes. The case was diagnosed streptococcic tonsillitis. Cabot¹⁴ reported a case of lymphadenitis and mononucleosis fol-

7 Pfeiffer, E. Drusenfieber, Jahrb f Kinderh **29** 257, 1889

8 Korsakoff, N. S. Beitrage zur Lehre des Drusenfiebers, Arch f Kinderh **41** 321, **42** 193, 1905

9 Lublinski, W. Beitrage zur Frage vom Drusenfieber, Ztschr f klin Med **62** 170, 1907

10 Neumann. Glandular Fever in Childhood, abstr, Arch Pediat **11** 691, 1894

11 Schleissner, F. Adenoiditis Acuta, ein Beitrag zur Lehre vom Drusenfieber, Wien klin Wchschr **24** 310, 1911

12 Marchand, F. Ueber ungewohnlich starke Lymphocytose im Anschluss an Infektionen. Deutsches Arch f klin Med **110** 359, 1913

13 Deussing, R. Ueber Diphtherieahnliche Anginen mit Lymphatischer Reaktion, Deutsche med Wchnschr **44** 513, 542, 1918

14 Cabot, R. C. The Lymphocytosis of Infection, Am J M Sc **145** 355, 1913

lowing infection by an unknown organism at the necropsy table. Another of Cabot's cases occurred during an epidemic of streptococcic sore throat, and a third patient had persistent boils.

Although nearly all the early observers, both in Germany and in England, considered glandular fever as a disease entity, they nevertheless gave considerable space to the differential diagnosis between this condition and atypical forms of influenza, measles, mumps and scarlet fever. The suspicion that glandular fever might be only an unusual form of some common infectious disease naturally influenced ideas as to etiology. To most authors the condition, if not a true entity, seemed to resemble atypical scarlatina more closely than any other disease. Cervical adenopathy is of course, very common in scarlet fever, and Tileston and Locke¹⁵ have since (1905) shown that in the second, third and fourth weeks of scarlet fever there is gradual rise in the percentages of mononuclear cells until they equal or often considerably exceed the number of granulocytic cells. In some of our own cases the throat was quite reddened, while in one there was a very temporary erythematous flush to the skin, and one patient developed an hemorrhagic nephritis.

It seems to us that in evaluating the evidence favoring a streptococcic etiology in glandular fever, we must first exclude all cases in which there is reasonable doubt as to the diagnosis. The fatal case reported by Koisakoff⁸ in which streptococci were demonstrated in the glands did not occur during an epidemic, and the fever was quite irregular from the first. The same may be said of the case with streptococcic meningitis. Since Neumann's¹⁰ series of cases, suppuration has been excessively rare in glandular fever, and some recent observers would exclude all cases that suppurate. Blood studies were not reported by either Koisakoff⁸ or Neumann¹⁰. Maichand's¹² case presents an interesting picture of lymphoid hyperplasia and bone marrow exhaustion occasionally seen in severe sepsis. We have had two such cases but we do not consider them in any way related to glandular fever. Turk's² case in all likelihood was either sepsis with bone marrow exhaustion or acute aleukemic leukemia, and clinically because of purpura and a peculiar infiltration of the lip it resembled more closely the latter. Cabot's¹¹ cases were also sporadic and he himself did not consider them to be glandular fever. With all dubious evidence removed, there may still be cause for a well grounded suspicion that streptococci are etiologically related to glandular fever but the facts are not numerous or impressive.

Koplik suggested that the infection might be gastro-intestinal, being conveyed to the glands of the neck by the thoracic duct. This theory

15 Tileston, W., and Locke, E. A. The Blood in Scarlet Fever, *J. Infect. Dis.* 2: 375, 1905.

seems to have presented itself because in a large percentage of the cases adenopathy was first noted in the cervical glands of the left side, especially just above the clavicle. An epidemic thought to be spread by milk was reported by Jackson¹⁶. Recent observers have not seemed to note the same regularity of onset in the left cervical glands which was stressed by earlier writers and there seems to be no constant gastro-intestinal symptoms associated with the condition.

Some clinicians, notably Lublinski⁹ and Turk,² felt that there was some relation between glandular fever and status thymolympathicus. To us the relation seems remote, indeed, and since status thymolympathicus is perhaps one of the least understood conditions in medicine at present, its association with glandular fever is neither helpful nor justifiable.

Jamison⁶ reminds us that interest has been aroused in glandular fever following both great epidemics of influenza.

In 1918 Deussing¹³ reported three cases of membranous angina associated with enlarged glands and an absolute mononucleosis. Positive cultures for diphtheria bacilli were obtained in each case and antitoxin was given with ultimate recovery. Virulence tests on the organisms were not reported. Coon¹⁷ in 1922 cultured a diphtheroid organism from a gland in a rather typical case. The material for culture was obtained by injecting saline solution into the gland and then withdrawing it. Our own results showed that throat cultures were taken in seventeen cases. In six of these diphtheria-like organisms were found, but none of them were proved to be virulent. A diphtheroid bacillus was also found in the blood culture of one of our patients. This organism grew in the bouillon and on all of the three blood agar plates. A similar diphtheroid was cultured from four of the six glands removed.

The evidence favoring a diphtheroid organism as the direct etiologic agent in glandular fever may be more apparent than real. It must not be forgotten that diphtheroids are a very frequent chance observation in throat cultures, that such organisms frequently contaminate mediums coming supposedly from the cotton stoppers, and that similar bacilli have been isolated from lymph glands and other tissue in a long series of diseases, most notably scarlet fever and Hodgkin's disease. When first isolated from the lymph glands in scarlet fever, they were thought to have an etiologic relationship to that disease, and the same was true of Hodgkin's disease. We therefore do not accept the presence of diphtheroid organisms in the lymph glands as proof of their etiologic relationship with the disease process that is present. Coon¹⁷ found his strain of organisms to be pathogenic for and recoverable from guinea-pigs but

16 Jackson G S. The Glandular Fever of Childhood, *Lancet* 2 979, 1897

17 Coon, H M, and Thewlis, E. Infectious Mononucleosis, *Wisconsin M J* 21 191 (Oct) 1922

we have been unable to substantiate his findings in this regard. That some diphtheroid bacilli do have a degree of pathogenicity is shown by the fact that one of us recently isolated such organisms in pure culture as the only organism present in an abscess of the thyroid gland. It is difficult to understand how these or any other organisms could lead a purely saprophytic existence within the lymph glands, but their relationship to the many diseases with which they have been associated is not definitely known.

Bloedorn and Houghton¹⁸ found Vincent's organisms in three of their four cases and suggested the possibility of a relationship between the two conditions. Similar observations were reported in three of Longcope's³ cases as well as in some other isolated instances.

Reference to our observations will show that spirochetes and fusiform bacilli are frequently found both along the gum margins and associated with definite membranous lesions in glandular fever. The frequent chance finding of such organisms in conditions unrelated to glandular fever seems to demonstrate the fact that Vincent's organisms, like the pyogenic cocci and diphtheroid bacilli, though often present in the mouth or throat of patients with glandular fever, are by no means of necessity associated etiologically with the condition in question. The possibility of glandular fever being a spirochetal disease of any type seems rather remote since six of our patients developed the disease while under active antisyphilitic treatment with arsenic and mercury, and since the dark field study of the excised glands failed to reveal spirochetes.

From the foregoing considerations it is obvious that we can have at the present time only preconceived notions as to the etiologic agent in glandular fever. We are therefore not attempting any interpretation of the mass of conflicting and inconclusive evidence at hand.

EPIDEMIOLOGY

Reports of glandular fever in epidemic form are numerous. Pfeiffer⁷ spoke of the condition as occurring in small "house" epidemics and affecting only children. Reports of similar small epidemics affecting families or otherwise closely associated children were numerous in the twenty years following Pfeiffer's description of the condition in 1889. Williams,¹⁹ Coutts,²⁰ Fisher,²¹ Chapman,²² Matheson,²³ Jackson¹⁶ and

18 Bloedorn, W. A., and Houghton, J. E. The Occurrence of Abnormal Leukocytes in the Blood in Acute Infections, *Arch. Int. Med.* **27** 315 (March) 1921.

19 Williams, D. A Note on the Glandular Fever of Childhood, *Lancet* **1** 160, 1897.

20 Coutts, J. A. The Glandular Fever of Childhood, *Lancet* **1** 346, 1897.

21 Fisher, T. The Glandular Fever of Childhood, *Lancet* **1** 407, 1897.

22 Chapman, C. W. The Glandular Fever of Childhood, *Lancet* **1** 555, 1897.

23 Matheson, J. K. Glandular Fever, *Lancet* **1** 192, 1904.

Byers²⁴ reported small epidemics from England, while Hesse,²⁵ Hoerschelmann²⁶ Schleissner,¹¹ Lublinski,⁹ Marrimon,²⁷ Neumann¹⁰ and others gave accounts of similar epidemics in Germany. Korsakoff⁸ reported one large and some small epidemics from Moscow, and while the French literature of the time contained a few accounts of epidemics, there seemed to be a consensus of opinion among French clinicians that the condition was not a true disease entity. Among the larger epidemics are those reported by West,²⁸ ninety-six cases in children in eastern Ohio, Korsakoff,⁸ fifty-four adult cases among Russian soldiers, Tidy and Daniel,²⁹ twenty-four cases occurring in a boys' school in England, Guthrie and Pessel,³⁰ about 300 cases from a boys' school in New Jersey, Gilbert and Coleman,³¹ more than 100 cases from New York State, and our own epidemic of thirty-two adult cases. In the later epidemics, blood studies have been made which seem to show the identical nature of glandular fever and infectious mononucleosis. Many other small epidemics that have never been reported have come to our attention, especially in the last year.

From our studies on apparently healthy medical students during the epidemic, we have been led to believe that the infection is often much more widespread than is appreciated and that many of our own as well as other, sporadic cases are only the more marked instances of a small epidemic, many of the cases in which are so mild as to escape notice.

The occurrence of these very mild unrecognized cases has made it difficult to follow accurately the spread of the infection or to ascertain the incubation period. In cases with known exposure and sudden onset, the incubation period seems to vary between five and nine days. It should be noted that this period of incubation is about midway between that of scarlet fever, diphtheria and influenza on the one hand, and measles, mumps and varicella on the other.

Children are no doubt more easily affected than young adults, and persons past middle life, rarely develop the condition, at least clinically. Sex has little influence though the larger epidemics have been among males.

24 Byers, J. W. Glandular Fever, *Lancet* **1** 84, 1904.

25 Hesse, B. Zur Casuistik des Pfeiffer'schen Drusenfiebers, *Jahrb f Kinderh* **42** 28, 1896.

26 Hoerschelmann, E. Casuistischer Beitrag zur Frage vom Drusenfieber, *Jahrb f Kinderh* **38** 14, 1894.

27 Marrimon. Ueber das Drusenfieber bei Kindern abstr., *Arch Pediat* **11** 691, 1894.

28 West, J. P. An Epidemic of Glandular Fever, *Arch Pediat* **13** 889, 1896.

29 Tidy, H. L., and Daniel, E. C. Glandular Fever and Infective Mononucleosis, *Lancet* **2** 9 (July 7) 1923.

30 Guthrie, C. C. and Pessel, J. F. An Epidemic of "Glandular Fever" in a Preparatory School for Boys, *Am J Dis Child* **29** 492 (April) 1925.

31 Gilbert, Ruth and Coleman, M. B. Laboratory Findings in an Epidemic of Glandular Fever, *Am J Hygiene* **5** 35 (Jan) 1925.

The usually very mild nature of the affection, together with the great difficulty in establishing the diagnosis in very mild cases, lead us to consider isolation of cases as impracticable

SYMPTOMATOLOGY AND PHYSICAL OBSERVATIONS

The individual symptoms and their relative frequency can best be seen by reference to table 1. Symptoms not tabulated here have been met with more or less frequently by other observers. It should be emphasized that any combination of symptoms with all degrees of severity may be manifest.

The same applies to the physical observations. The number and distribution of enlarged lymph glands is most variable. In some cases it is necessary to search carefully to find the enlarged glands while in others the contour of the neck is completely obliterated and the axillae and groins actually bag down with masses of enormously enlarged, very soft and tender glands. Usually some glands are present at the onset, but the number and size often increases for the first few days. We have noted in a fair percentage of the cases that the initial adenopathy is confined to the left cervical region with an involvement later of other groups. The glands vary from a few millimeters to 4 cm. in diameter. In our cases the larger glands have nearly always been soft and spongy. The glands that were removed always proved to be larger than had been anticipated, probably because of their very soft consistency. Tenderness in the glands varies from day to day, but usually is most marked at, or soon after, the onset. At times the tenderness is only moderate, but many cases have been seen in which the glands were too tender to allow of satisfactory palpation. Our apprehension regarding suppuration is becoming less and less, because of the extreme rarity of its occurrence in reported cases, and because we have repeatedly seen large groups of exquisitely tender glands subside without surgical intervention. The appearance of the throat is often characteristic. The lymphoid follicles of the pharyngeal wall are hyperplastic and have a peculiar translucent appearance. The frequent occurrence of membranous angina should not be overlooked. In such cases the membrane is a dirty gray color and usually occurs over the tonsils and pillars and occasionally over most of the buccal and pharyngeal mucous membranes. There is nothing in the gross appearance of the membrane which could be relied on to rule out diphtheria, scarlatinal angina or Vincent's angina. The spleen, when enlarged, is soft and elastic with a rounded edge.

Modes of Onset and Clinical Course—1 The onset may be sudden with a high fever, either of the septic type or more or less sustained for a few days. Chills are rather frequent. In such cases there are associated many of the symptoms that are more or less common to all acute

severe infections, such as headache, prostration, nausea, vomiting, etc., but there are no localizing signs of infection. There usually is a leukocytosis with a high percentage of neutrophilic polymorphonuclears. Such cases often show little adenopathy.

2 A second type of onset is with fever, sore throat and membranous angina. In these cases the fever usually is less than in the foregoing type. Constitutional symptoms also are less marked, and a few glands usually are present from the beginning. The initial blood count often shows a moderate leukocytosis with about the normal percentage of polymorphonuclear cells.

3 Another type of onset is with some fever and tender glands but with nothing in the throat except the granular appearance described above.

4 The initial symptoms may be entirely abdominal with pain, fever and leukocytosis, and glands appear days later.

5 The fifth type of onset is so insidious and the symptoms so mild that the patient neither stops work nor consults a physician. This group includes such cases as we found among medical students in whom blood smears showed a mononucleosis, and in some of whom enlarged and slightly tender glands were found on careful examination.

We have not observed any particular relationship between the type of onset and the subsequent course. Convalescence is often markedly protracted. The glands persist for a variable period. In some cases they return to about normal size in a few days and apparently remain normal. In others the glands remain slightly enlarged for a period of months or even years. In still others there are periods in which the glands reenlarge and become tender at variable periods after the initial attack. Such recurrences are often associated with some fever and many of the symptoms of the original infection. We have followed one patient through four such attacks in the last three years. The spleen is usually enlarged only for a few days, but we have one patient in whom the spleen was much enlarged at the onset and has remained palpable for seven years without other known cause.

The blood count is often very slow in returning entirely to normal though most of the abnormal cells disappear after the first few weeks. Blood counts have been made at many intervals from a few weeks to seven years after the initial infection and in practically all we have found some abnormal mononuclear cells, although the percentages often have not been high. Exacerbations or recurrences are associated with an increased mononucleosis.

Pathology—The difficulties in pathologic diagnosis will present themselves in those conditions characterized by extreme lymphoid hyperplasia, in which no etiologic factor can be demonstrated and there is no charac-

teristic histologic appearance. Many of the diseases that clinically resemble glandular fever can be diagnosed by the removal of a gland that contains either the etiologic organism or some characteristic histologic appearance, for example, tuberculosis, syphilis, typhoid fever and tularemia. The pathology of lymph glands, hyperplastic as the result of acute or subacute infections, is little known, and the difficulties that might arise in differentiating histologically such conditions from glandular fever are not appreciated. The hyperplasia in glandular fever is extreme and many atypical lymphoid cells are evolved. The process compresses the sinuses and obscures the architecture, but we have no assurance that this condition cannot be simulated by other acute infectious lymphadenopathies. The histologic diagnosis of glandular fever must not therefore be relied on too implicitly. The hyperplasia of the lymph nodes and the atypical cells evolved are more marked in glandular fever than in any other acutely enlarged lymph nodes that we have studied.

The malignant lymphomas (lymphocytic leukemia, Hodgkin's disease and lymphosarcoma) are distinct problems in histologic differentiation. In those cases of malignant lymphoma in which the architecture is obscured and the peripheral sinuses obliterated by lymphocytic or lymphoblastic cells of uniform size the diagnosis is easy. But as is often the case in so-called Hodgkin's disease the cells may vary in shape and size and such histology differs but little from that seen in glandular fever. In these instances the helpful points are. In glandular fever some sections are apt to show remains of germinal centers, the sinuses are still in evidence and the very large tumor cells of Hodgkin's disease are not present. Also in glandular fever there is no evidence of necrosis or fibrosis.

Blood—The attention of a few clinicians and hematologists has recently been focused on glandular fever, largely because of the interesting blood abnormalities. Total leukocyte counts, differential findings and abnormal colorless elements have been discussed by many authors including Tuik,² Sprunt and Evans,⁴ Bloedorn and Houghton,¹⁸ Longcope,³ Tidy and Daniel,²⁰ Downey and McKinlay⁵ and others.

Our own observations as to the total leukocyte counts have for the most part, been in accord with those of previous authors. As a rule there is a leukocytosis some time during the course of the disease, usually at the onset. In the vast majority of the cases the increase is only moderate, that is not above 20,000 per cubic millimeter. In two of the fifty cases, counts above 20,000 were found. Total white counts below the average normal were met with rather frequently, often during convalescence. This point has not been especially stressed in the literature to date.

An interesting feature in the differential counting is the fact that the percentage of mononuclear cells averages much higher in sporadic cases

than in epidemic cases. This observation is true for the epidemics reported by Tidy and Daniel,²⁹ Guthrie and Pessel,³⁰ Gilbert and Coleman,³¹ as well as our own. During an epidemic there are many cases in which there is a definite acute febrile onset and in such instances there is also an initial polymorphonuclear increase. Although there is no rigid parallel between the degree of fever and the polymorphonuclear increase, there is at least a definite relationship. The mononucleosis gradually develops as the fever subsides. In most cases this is not only a relative increase made evident by the decrease in the polymorphonuclear elements, but there is also a definite absolute increase in both numbers and varieties of abnormal mononuclear cells. A somewhat similar tendency was noted by Tileston and Locke¹⁵ in the blood of patients convalescing from scarlet fever.

We feel that the apparent discrepancy in the degree of mononucleosis reported in sporadic and in epidemic cases can be readily explained on the following basis. The differential diagnosis between glandular fever and nonspecific upper respiratory infection with cervical adenitis is notoriously difficult, and consequently many cases with cervical adenitis are dismissed as "upper respiratory infection" when the first blood count shows a polymorphonuclear increase. In the presence of an epidemic these cases are apt to be more carefully followed and subsequent blood examinations reveal a mononucleosis of moderate to marked degree. In many sporadic cases, the onset is some time before their application for treatment which is sought only because of persistent glands, slight febrile attacks or continued and troublesome symptoms and consequently blood counts are not done during the acute febrile onset.

American clinicians and hematologists are quite well agreed in considering the mononucleosis of glandular fever as being due to an absolute increase in lymphocytic cells, many of which are forms not commonly seen in the blood of normal subjects. Baader,³² Hopmann³³ and some other German writers feel that many of the abnormal cells are monocytes, and occasionally one sees reports of apparently very similar blood pictures in which the abnormal cells are called myeloblasts.

The following is a general description of the abnormal cells. The size varies from but little larger than the small lymphocyte to cells as large or even larger than the largest cells of normal blood which probably have their origin in the reticulo-endothelial system. The inner structure of the nucleus in some is like that of the normal lymphocyte in that it is made up of irregular bands of chromatin, which give it a

32 Baader, E. Die Monocytenangina, *Deutsches Arch f klin Med* **140** 227 (Sept) 1922.

33 Hopmann, R. Akute Infektiose Stammzellenvermehrung im Blute mit Heilung. *Deutsches Arch f klin Med* **142** 196, 1923.

rather wavy appearance. Nucleoli are not at all common. The outline of the nucleus varies markedly, being round or oval, bean or horse shoe shaped, or irregularly lobulated and indented. Occasionally nuclei are met with in which there is a very marked condensation of chromatin near the periphery giving a suggestion of the clock faced appearance seen in plasma cells. In one case Downey⁵ found cells which, in appearance and staining reaction, resembled closely the stem cell. In such cells the nuclei are round with a rather uniform dispersion of fine chromatin threads and nucleoli are present. The chromatin arrangement within the nuclei of many of the cells in our series was very close to that seen in normal monocytes.

The cytoplasm of the cells under discussion varies somewhat in amount but is usually more abundant than in the normal lymphocyte. In some of the cells the cytoplasm stains quite deeply basophilic, while in others (in our experience, the majority) there is only a faint outline of blue about the periphery while the remainder of the cytoplasm is almost hyaline. Stained with modifications of the Romanowski method there is great variation in the number and size of azurophil granules. In some cells there are no granules, while in others there are a few large rigidly spherical granules and in still others there are vast numbers of very small irregularly shaped acidophilic granules which are so very small and are so arranged as to resemble a reticulum.

From the first we have had great difficulty in classifying the abnormal cells because of the fact that all gradations between small lymphocytes and normal monocytes were present. Two methods for differentiation presented themselves, viz., peroxidase reaction and McJunkin stain. Some cells having their origin in the reticulo-endothelial system contain a small amount of the peroxidase ferment, and when stained by the McJunkin method the cytoplasm resembles that of the neutrophilic polymorphonuclear leukocyte more than the lymphocyte. Vital staining was not done though we feel that it probably would give a more accurate index to functional activity than either of the foregoing methods. The study of fresh preparations will also be made in an effort to better establish the relationships of these abnormal cells. With most special stains and especially in the peroxidase reaction, the finer structure as seen with Wright's stain is not well brought out, so that individual cells cannot be well compared in the two stains. The percentages of cells showing the staining characteristics of monocytes were not especially high in any of the cases studied, varying from 6 to 12 per cent of the total number of leukocytes.

It would seem, however, that not all cells that are of endothelial or reticulo-endothelial origin can be identified by either the peroxidase reaction or the McJunkin stain. This is especially true of the large, irregularly outlined hyaline cells which are often seen in normal blood

and which often form as much as 75 per cent of the total circulating leukocytes in cases of glandular fever

In a discussion of the blood picture in glandular fever, the following facts seem to indicate a lymphogenic origin of the abnormal cells

- 1 Histologically the greatest activity in the lymph nodes is in the germinal centers and lymphatic cords

- 2 Cells resembling in size and shape the abnormal circulating elements are present in the germinal centers of the hyperplastic lymph glands, as well as in the lymph sinuses

- 3 The greatest and most consistent apparent pathologic change of the disease is in the lymph glands

- 4 Many of the circulating cells have the staining characteristics, the nuclear structure and the azure granules of lymphocytes

- 5 A very marked scarcity of normal circulating small lymphocytes is often an outstanding feature of the blood picture

As favoring an endothelial or reticulo-endothelial origin of these cells one might cite the following observations ³⁴

- 1 Mitotic figures are met with in the endothelial lining of lymph sinuses

- 2 Occasionally very high percentages (75 per cent) of the circulating cells are morphologically and in staining characteristics very similar to those of normal blood which are sometimes called hyaline cells and which McJunkin feels have their origin from vascular endothelium

- 3 The degree of mononucleosis is often not proportional to the degree of hyperplasia of superficial lymph nodes

- 4 The special staining methods that we have used are not specific enough to prove the nonendothelial nature of these cells and vital staining and investigation of the phagocytic and ameboid powers of these cells have not been done

- 5 Hematologists are not yet fully agreed as to the origin and status of that group of cells which are variously named transitional cells, large mononuclears, endothelial leukocytes, splenocytes, monocytes, etc. Reliable specific tests for this bizarre group of cells would be of great help in establishing the blood picture of glandular fever, since morphology alone is apt to lead one to false conclusions

After numerous unsuccessful attempts to arrive at a simple and accurate method for subdividing this group of abnormal colorless elements, we finally concluded to follow the example of Longcope in plac-

³⁴ J. Hatzieganu and I. Goia (Bull. et mem. Soc. med. d. hop. de Paris **2** 69 [Jan. 16] 1925) report a case of monocyte angina. Because of the response of the abnormal mononuclear cells to injections of epinephrine, the authors concluded that these cells were not lymphogenic.

ing all such cells in one large group to be spoken of as abnormal mononuclears. This course seems wise, for the present at least, for two reasons: first, because any attempt at dividing the abnormal cells into groups leads to stilted classifications based on slight morphologic differences, and varying with different observers, and, second, because according to the monolistic theory of blood origin the lymphocytes and monocytes are closely related and in some stages of embryonic life Maximow³⁵ has found all stages of transitional forms from lymphocytes to monocytes.

We are by no means sure that the blood percentages in glandular fever are significant of more than an acute nonsuppurative hyperplasia of lymph nodes. It has already been noted that a lymphocytosis is a common occurrence in convalescence from scarlet fever. Tileston and Locke did not try to correlate the degree of lymphocytosis with the amount of evident lymphatic hyperplasia, nor did they speak of the occurrence of abnormal lymphocytes in the blood. The mononucleosis of whooping cough is explained by Friedlander³⁶ as being due to hyperplasia of the tracheobronchial lymph glands. Typhoid fever and syphilis are associated with lymphoid hyperplasia, and exophthalmic goiter is often associated with some lymphoid hyperplasia as well as lymphoid infiltration of the thyroid gland. Many other less common conditions are associated with a lymphocytosis as well as hyperplasia of the fixed lymphatic tissue. It is usually considered that in such diseases the lymphocytosis is only relative and is made apparent by the scarcity of granulocytes. We have found in a great many cases of this sort that the lymphocytosis is in reality absolute, that is, more than 25 per cent of 8,000 or 2,000 cells. And now we come to the fact that many observers have noted the presence of abnormal mononuclear cells in the blood of patients with lymphocytoses and lymphoid hyperplasia from various causes. Naegeli³⁷ speaks of their occurrence in intoxications, such as Basedow's disease, as well as in infectious diseases, for example, typhoid fever. By a careful study of the stained blood, we were able to find variable percentages of pathologic lymphocytes in the blood of many patients in which there was no suspicion of glandular fever. This group included (1) three cases of serum sickness in which there was a marked generalized lymphadenopathic condition, (2) one case of streptococcal infection of the foot with inguinal adenitis, (3) one case of suppurative staphylococcal cervical adenitis, (4) several cases of diphtheria with cervical adenitis, (5) one case of septicopyemia with enlargement of the spleen and iliac lymph nodes, and (6) besides the foregoing, path-

35 Maximow, A. A. Relation of Blood Cells to Connective Tissue and Endothelium, *Physiological Rev.* 4: 533 (Oct.) 1924.

36 Friedlander, A. Whooping Cough, *Abt's Pediatrics* 6: 128, 1925.

37 Naegeli, O. *Blutkrankheiten und Blutdiagnostik*.

ologic lymphocytes of all varieties are frequently found in sinus infection with cervical adenitis. These observations have led us to the opinion that the observation of small numbers of even the most bizarre types of abnormal lymphocytes is of no significance except to point toward the presence of acute lymphoid hyperplasia in some part of the body. In other words, we believe that pathologic lymphocytes may enter the blood stream from lymph nodes that are hyperplastic from any cause. The migration of lymphocytes into the lymph sinuses and thus into the blood stream is no doubt best accomplished in those glands which are actively hyperplastic, but in which there is not much disturbance to the architecture of the gland. On this basis we should logically expect a rather marked migration from glands showing the pathologic picture seen in glandular fever, and little or no migration from chronic tuberculous lymph glands or those enlarged by metastatic malignancy. Acute miliary tuberculosis of lymph glands may cause hyperplasia without much destruction of the gland architecture and in this way explain the cases of miliary tuberculosis associated with the very high lymphocyte counts such as those reported by Landon³⁸ and also by Wiechmann³⁹.

According to Pappenheim,⁴⁰ cells of the type under discussion are old, because of the irregularly lobulated and indented nuclei, and are functionally active, because of the large amount of cytoplasm, which is at times granular and vacuolated. We have no grounds for either accepting or disputing this statement, and the abnormal cells in the blood of patients with glandular fever may have a definite function. We do feel, however, that these cells are not produced to combat any specific toxic principle which is found only in glandular fever. Their occurrence in most if not all other acute nonsuppurative lymphadenopathies makes such an assumption absurd. Also we are not able to agree with Turk² who felt that the abnormal lymphocytes entered the blood stream to replace polymorphonuclear cells which were not available for the blood because of temporary exhaustion of the bone marrow. The prompt polymorphonuclear response to foreign protein seen in four of our cases seems to prove that the bone marrow is not exhausted. Similar observations on one patient are reported by Hopmann³³. There is at present no known cause for either the entrance of the abnormal lymphocytes into the blood stream or the absolute decrease in the number of circulating granulocytes. We feel quite certain that some of the abnormal mononuclear cells originate in the hyperplastic lymph nodes. We have, however, no knowledge as to whether they are pushed into the lymph sinuses mechanically, or are attracted into the lymph by some chemotaxic substance.

38 Landon, J. F. Conditions Simulating Acute Lymphocytic Leukemia (Infectious Mononucleosis, Tuberculosis), *Am J M Sc* **170** 37 (July) 1925

39 Wiechmann, E. *Med Klin* **18** 1086 (Aug 20) 1922

40 Pappenheim, A. *Atlas der Menschlichen Blutzellen*

No single blood picture can be said to be typical of glandular fever because the abnormal mononuclear cells are so variable both in number and in variety, and the same cell types are found in other conditions. Routine blood examinations on any large group of patients will result in the observation occasionally of a marked mononucleosis, either relative or absolute. The frequency of lymphocytoses in diseases associated with acute lymphoid hyperplasia has long been recognized. The lymphoid hyperplasia may be due either to intoxications, such as exophthalmic goiter and serum sickness, or to such infections as whooping cough, typhoid fever or syphilis. Relative lymphocytosis is the rule in diseases associated with a leukopenia, but abnormal mononuclear cells are more common in those conditions in which there is an absolute increase in the lymphocytes. In severe sepsis with so-called bone marrow exhaustion, abnormal mononuclear cells are often encountered even though there is a very marked absolute decrease in all types of circulating colorless elements, with a relative lymphocytosis.

A few examples of mononucleosis, both relative and absolute, selected from the University Hospital records are given in table 7.

TABLE 7—*Examples of Mononucleosis, Both Relative and Absolute*

	White Blood Cells	Poly- morpho- nuclears	Lympho- cytes	Mono- cytes	Eosino- phils	Baso- phils
1 Whooping cough	36,800	18	80	2		
2 Typhoid fever	8,200	31	62	6	1	
3 Secondary syphilis	7,250	43	57			
4 Exophthalmic goiter	6,800	32	45	3		
5 Septicopyemia	3,500	20	80			
6 Vincent's angina with ter- minal septicemia	600	5	80	5		1

It is evident that each disease given in table 7 is an example of a relative lymphocytosis, that in the first four there is an absolute lymphocytosis, in the fifth the lymphocytes are present in about normal absolute numbers, while in the last case there is an absolute decrease in all types of white blood cells. The last two cases were febrile and the low leukocyte counts might be attributed to what is often spoken of as bone marrow exhaustion. Abnormal lymphocytic cells were found in each of these cases. In whooping cough many of the cells are large and have irregular nuclei, but because the disease usually occurs in young children in whom large irregular lymphocytes are quite common not much notice is taken of them. In the patients with typhoid fever, secondary syphilis and exophthalmic goiter, the abnormal lymphocytes formed a rather small percentage of the total, possibly because the lymphoid hyperplasia was neither as acute nor as marked as in the other cases. The septicopyemia in the fifth patient resulted from thrombosed hemorrhoidal veins and there was marked enlargement of the spleen and the iliac lymph

nodes In this patient most of the lymphocytes were large and irregular in outline The patient with Vincent's angina had a long drawn out septic course with a marked generalized lymphadenopathic condition and a staphylococcus was isolated from the blood stream before death The total leukocytes in this case reached the extremely low level of 50 per cubic millimeter and many of the lymphoid cells were abnormal

It is apparent that a differential diagnosis between any of the foregoing conditions and glandular fever could be readily made clinically in spite of the more or less similar blood percentages The tendency of abnormal lymphocytes to enter the blood stream in such cases with lymphoid hyperplasia should, however, not be overlooked

DIFFERENTIAL DIAGNOSIS

The factors responsible for diagnostic difficulties are the various modes of onset and the persistence of enlarged glands

1 Cases with the septic type of onset must be differentiated from pyogenic septicemia, typhoid fever, miliary tuberculosis, acute Hodgkin's disease, acute leukemia, influenza, dengue, epidemic thyroiditis and tularemia

2 Those associated with fever and membranous angina may resemble diphtheria, scarlet fever, Vincent's angina or follicular tonsillitis

3 Cases in which there is only fever, tender glands and a granular throat with moderate constitutional symptoms may be confused with paranasal sinus disease or mumps

4 If abdominal pain and tenderness are the first outstanding symptoms, appendicitis may be considered

5 Cases with very insidious onsets and few symptoms are usually entirely missed or are seen late because of persistent glands

Those cases in which the adenopathic condition persists and is the outstanding feature have to be differentiated from other conditions associated with enlarged lymph nodes, for example, the malignant lymphomas (including chronic lymphocytic leukemia, Hodgkin's disease and lymphosarcoma), tuberculous adenitis, syphilis and Still's disease

1 *Septic Onset Without Localizing Symptoms or Signs*—By a study of the temperature chart and blood percentages in case 2 one is impressed by the similarity to septicemia In fact our impression of septicemia in this case was changed only by the subsequent course and blood percentages and should another such case present itself in the absence of a recognized epidemic, we should still be unable to make the diagnosis in the first few days The only aid to diagnosis in such instances is the negative blood cultures, and it was in this case that a diphtheroid was isolated from the blood stream

Typhoid fever may be suggested by the splenic enlargement and the fever, especially if it is sustained, but the history, the leukocytosis and cultures of the blood, stools and urine should suffice to rule out typhoid fever.

In miliary tuberculosis the blood picture may approach very closely that seen in any stage of glandular fever, but the history and the profound nature of such a tuberculous infection are helpful points.

Acute Hodgkin's disease presents a difficult clinical problem. The glands, the spleen, the fever, the negative blood cultures and the diening sweats are the same in the two conditions. The fever in either condition is apt to subside rather readily. Age, sex and occupation are not very helpful. The glands in Hodgkin's disease are apt, however, to be more firm and less tender than in glandular fever and the anemia characteristic of the former is rare in the latter condition.

Acute Leukemia We have not seen a case of glandular fever in which the clinical picture approached that seen in acute leukemia, although Downey and McKinlay⁶ report one such patient. At any rate petechia, hemorrhages from the mucous membranes and a rapidly developing anemia must be rare in glandular fever. Again, in glandular fever the febrile period is at the onset, at which time the glands are tender, while the subsequent course is one of improvement. In acute leukemia there is a gradual downward progression with increasing fever, anemia and hemorrhages and as a rule the glands are not tender. Certain individual blood cells may be found in glandular fever which resemble the very unique elements of acute leukemia, but in our experience a differential study of 100 cells has been ample to establish the diagnosis. In no case of glandular fever have we encountered anything like the number of uniform, large unique cells seen in acute leukemia. In consulting practice we have found leukemia and glandular fever confused but twice, once a case of glandular fever was diagnosed leukemia on the blood percentages and histology of an excised gland, and the other was a case of leukemia which was mistaken for glandular fever because it developed during a small epidemic of the latter condition.

Influenza The similarity here is only in the fever, symptoms and epidemic nature. No doubt many cases of glandular fever are wrongly diagnosed as influenza and we have heard of local epidemics in this section of the country which were called glandular influenza.

Dengue This is an acute febrile epidemic disease of short duration associated with a lymphadenopathic condition, a leukopenia with a relative lymphocytosis and "break bone" pains. It resembles glandular fever except in the "break bone" pains and in its etiology. It is a tropical or subtropical disease prevalent in warm damp regions and the infectious agent is introduced by the bite of a mosquito.

Epidemic thyroiditis is an infectious disease occurring in South America, caused by a trypanosome, and associated with a generalized adenopathic condition and enlargement of the thyroid gland. A few cases of glandular fever with enlargement of the thyroid have been noted, but certainly the patients did not have trypanosomes in their blood streams.

Tularemia More and more cases of this disease are being recognized throughout the United States. It is an infectious disease associated with an adenopathic condition. The blood percentages in tularemia have not as yet been carefully studied, but no outstanding examples of mononucleosis have been reported, although an increase in monocytes or endothelial leukocytes has been reported in a few cases. In tularemia there is often a very characteristic local lesion at the site of inoculation. *Bacterium tularensis* is quite easily demonstrated by animal inoculation and the demonstration of its presence should be required to differentiate mild nonsuppurative cases of tularemia from glandular fever, especially when *Bacterium tularensis* has not been proved to exist in rodents and insects of the vicinity in which the case occurs.

2 Febrile Cases with Membranous Angina—Diphtheria has been differentiated from glandular fever in our cases with considerable difficulty. Cervical adenitis is quite common in diphtheria though it is usually not especially marked at the onset. Nonvirulent, diphtheria-like bacilli are quite frequently found in normal throats and seem to be especially frequent in glandular fever. We know of no reliable method for determining the nature of a membranous angina by its gross appearance alone. Only suggestive and often very unreliable evidence can be thus obtained. The difficulties that we encountered are perhaps best shown by the fact that we gave antitoxin to six patients who had clinical signs suggestive of diphtheria and "suspicious cultures" and later found that the organisms were not virulent and each patient developed a more or less generalized lymphadenopathic condition with a characteristic blood picture.

Scarlet Fever The angina and adenitis may be similar to that seen in glandular fever. A slight flush occasionally occurs in glandular fever, but we have never seen anything like a typical scarlatinal rash. A similar tendency in the blood percentages during convalescence has been noted in the two conditions. In cases of scarlet fever in which the rash and "strawberry tongue" have subsided and desquamation has not yet begun the differentiation may be impossible.

Vincent's Angina The spirochetes and fusiform bacilli of Vincent's angina are probably always present in glandular fever with membranous angina so that the differentiation must be made on the adenopathic condition and subsequent course, especially the blood percentages.

Follicular Tonsillitis No conditions seen in our glandular fever patients have resembled follicular tonsillitis very closely, though several have developed small peritonsillar abscesses. These abscesses were, for the most part, small and resembled the small buried pockets of cheesy material commonly seen about the tonsils in Vincent's angina.

3 Cases with Fever, Tender Glands and a Glandular Throat—Paranasal sinus disease enters very frequently into the differential diagnosis of such cases. In acute sinusitis, the symptoms and roentgen-ray and nasoscopic findings are usually sufficient to establish the diagnosis. A very high percentage of the people of the state of Iowa have some chronic paranasal sinus disease, and it is often impossible to prove or disprove the etiologic relationship of such infection to enlarged cervical glands. The glands of chronic sinus disease, however, are usually rather firm and not tender, while in glandular fever the swollen lymph nodes are soft and tender and some are almost invariably found in regions receiving no drainage from the sinuses.

Mumps may resemble glandular fever superficially, especially if the swelling is confined to the submaxillary glands.

4 Insidious Cases with Few Symptoms—The important point in the diagnosis of this group is to rule out normal persons who have glands that are enlarged from previous infection. The rules governing the normal percentages of the various types of colorless blood cells are by no means iron-clad. Drinker,⁴¹ in *The Oxford System of Medicine*, gives tables to show the normal variation in lymphocytic percentages and warns against attaching too much significance to a moderate lymphocytosis.

Our own observations on a class of medical students during an epidemic are in accord with the observations of Guthrie and Pessel, who noted enlarged glands months after the epidemic in a large proportion of exposed boys in whom few or no clinical symptoms were manifest during the epidemic. Judging from these observations, we might logically conclude that there usually are a large group of very mild unrecognized cases associated with an epidemic, only the more severe cases of which are recognized. The importance of such mild cases in spreading the disease cannot be overemphasized, especially if any attempt at isolation or segregation is to be made. The difficulties in determining just which cases are to be called glandular fever and which normal will be appreciated when we try to divide the following group of patients into two classes, one having glandular fever and capable of transmitting it and the other class to be called normal and to be considered not capable of transmitting the disease to others. It should be remembered that only the first group had symptoms severe enough to bring them to the

⁴¹ Drinker, C. K. *Oxford System of Medicine*, vol. 2, p. 541.

outpatient department, even though they were present in the hospital every day. Twelve cases with mononucleosis symptoms and enlarged glands, nineteen cases with mild symptoms of mononucleosis and enlarged glands, nineteen cases with mild symptoms of mononucleosis but no enlarged glands, twenty-five cases with mononucleosis, no symptoms and no enlarged glands, and two cases with no mononucleosis symptoms or enlarged glands.

Cases with a persistent adenopathic condition are more easily differentiated from cases with similar conditions than are the acute cases at the time of onset.

Malignant Lymphomas (a) **Chronic lymphocytic leukemia** This condition is more common in old people, the onset very insidious and the glands more firm and less tender than in glandular fever. Fever may be present with intercurrent or terminal infections and a definite anemia is a part of the picture. There would be little danger of confusing the stained blood smears of chronic lymphocytic leukemia and glandular fever. The great predominance of nearly normal small lymphocytes in the former condition is in direct contrast to the bizarre group of abnormal large cells seen in the latter.

(b) **Hodgkin's disease** "Pel-Ebstein" fever with sweats in this condition forms a possible source of confusion. The history of the case, the anemia, the hard, nontender glands are not similar to the findings in glandular fever.

(c) **Lymphosarcoma** This group of cases, which has been separated clinically from the rest of malignant lymphomas, is easily distinguished by the hard glands, often conglomerate, causing obstructive edema and the rapid course of the disease.

Tuberculous Lymphadenitis The more chronic types of this affection do not produce the blood picture of glandular fever and the history together with the consistency of the glands, their location and tendency to break down are all differentiating features. The tuberculin reaction might be of aid.

Syphilis The adenopathic condition in syphilis may be marked and generalized, but the history and serologic tests and evidence of syphilis elsewhere will establish the diagnosis. We have no explanation for the rather frequent occurrence of glandular fever in patients under antisyphilitic treatment. It has been suggested that a Herxheimer reaction might account for the adenopathic change in this group of cases, but we noted during the epidemic that these patients were as apt to transmit the disease as any other patients. Jameson⁴² has reported three cases,

⁴² Jameson, R. E. Vincent's Angina Developing During the Time Neoparsphenamine Was Being Administered Intravenously in Two Known Cases of Luetic Infection and in One Case Diagnosed Syphilis from Clinical Symptoms. *J. Iowa State M. Soc.* **15**: 264 (May) 1925.

one of which was fatal, in young men while under antisyphilitic treatment. Blood counts were not done in his cases, but the clinical description corresponded to our own cases. White⁴³ also reported a severe case which developed while the patient was receiving antisyphilitic treatment.

Still's disease or infantile arthritis deformans may produce the adenopathic condition and the enlarged spleen. Large lymphoid cells, some of which have slightly irregular nuclei, are common in children but the history and deformities of Still's disease are quite characteristic.

STATUS

Conservative clinicians are rather slow to accept glandular fever as a disease entity because of the lack of a clear cut, uniform clinical picture, because other infectious diseases may so very closely simulate glandular fever, because no etiologic agent has been demonstrated, and because the disease has not been definitely transmitted experimentally. The truth of these contentions is not to be denied. An additional feature that we have found to be rather disturbing is the great range in the severity of the condition.

There is, however, a considerable amount of evidence which points to the existence of a rather definite disease entity in this group of cases. Certainly not all of the cases reported under the name glandular fever or some one of its synonyms can be proved to belong to one disease entity. But after all questionable cases are eliminated there remains a considerable group which, though not entirely uniform, have many features in common. A few points favoring the existence of a true disease entity may be mentioned: (1) the epidemic nature of the disease, (2) the enormous enlargement of the lymph glands which histologically show extreme hyperplasia and many atypical lymphoid cells, (3) the occurrence of relative increases in the circulating mononuclear cells (above 80 per cent in many cases and 99 per cent in one case) which are not met with in other infectious diseases, (4) the large percentage of abnormal cells, both circulating and in the lymph nodes, and (5) the very widespread occurrence of the disease throughout the temperate zones.

A study of the epidemic as well as some of the sporadic cases reported will tend to convince even the most conservative as to the existence of a symptom complex which may be called glandular fever. We are not able at the present time to formulate a set of qualifications which when fulfilled, establishes the diagnosis as glandular fever and at the same time includes all cases of glandular fever and excludes all other infectious

43 White, E. C. Lymphadenosis, an Acute Benign Disease Simulating Acute Leukemia, U. S. Naval M. Bull. **22** 302 (March) 1925.

diseases The three observations most frequently noted are fever, a lymphadenopathic condition and mononucleosis When in addition to these we have the presence of an epidemic the diagnosis can safely be made It must be borne in mind that all degrees of severity are apt to be present in any epidemic and the same is no doubt true of sporadic cases Some of these are very typical and marked examples, while others are so mild or atypical that the diagnosis in individual cases may be impossible It is this perfectly gradual gradation from the most severe to the most mild that has caused us to wonder just how many and in what degree of severity the symptoms, signs and laboratory observations must be present in order to establish the diagnosis And again, if the very mild atypical cases which seem to be part of an epidemic are not specific and are not part of a disease entity, then why should we consider the most marked and severe cases in the same epidemic as integral parts of a true entity? The final answer can come only from the demonstration of a specific etiologic agent or from the repeated successful experimental transmission of the disease

In the absence of proof and in the presence of such conflicting evidence, it seems to us that it would be highly unwise to be too dogmatic in regard to glandular fever being a disease entity That such a symptom complex exists there can be no doubt For purposes of study it seems best to set this group of cases apart from other similar infectious diseases, whether or not they are eventually proved to comprise a single disease entity

NAME

The disease process under consideration has been designated by a long series of names most of which have been more or less descriptive Some of the synonyms are as follows glandular fever (Pfeiffer⁷), infectious mononucleosis (Sprunt and Evans⁴), acute benign lymphoblastosis (Bloedorn and Houghton¹⁸), acute benign leukemia (Cross⁴⁴), acute lymphadenosis (Downey and McKinlay⁵), acute sublymphatic lymphocytosis (Turk²), and monocyte angina (Baader³²) Other authors have reported somewhat similar conditions under descriptive titles without definite names Examples are idiopathic enlargement of lymph glands (Filatow¹), acute lymphatic leukemia with apparent cure (Ireland and Ruhrah⁴⁵), a case resembling acute lymphatic leukemia ending in recovery (Hall⁴⁶), lymphocytosis of

44 Cross, J. G. Conditions Simulating Acute Leukemia, *Minnesota Med* 10 579 (Oct) 1922

45 Ireland, Bactjer and Ruhrah. A Case of Lymphatic Leukemia with Apparent Cure, *J A M A* 65 948, 1915

46 Hall, A. J. A Case Resembling Acute Lymphatic Leukemia Ending in Recovery, *Proc Roy Soc Med* 8 15, 1914-1915

sepsis (Cabot¹⁴), and acute infectious increase of stem cells in the blood with recovery (Hopmann²⁷)

Pfeiffer's term, glandular fever, has priority over all others and has been more used than any other name. Infectious mononucleosis has been a rather popular name in this country since its introduction by Spiunt and Evans in 1920. But since 1920 there has been accumulated a mass of evidence that seems to prove the identical nature of glandular fever and infectious mononucleosis. In our experience neither name in its descriptive sense is applicable to all cases, since often the superficial adenopathic condition is almost negligible, and in other cases the mononucleosis is not an outstanding feature. In order to include all cases both epidemic and sporadic we have used the combination of both names as it appears in the tenth edition of Osler's Principles and Practice of Medicine.

SUMMARY

1 The literature contains ample descriptions of a fairly well defined symptom complex which may be called glandular fever (infectious mononucleosis)

2 This is an acute infectious disease of unknown etiology, usually of short duration, characterized by fever, enlarged lymph glands, and the occurrence of numerous abnormal mononuclear cells in the circulating blood

3 Streptococci, diphtheroid bacilli and the spirochetes and fusiform bacilli of Vincent's angina have been mentioned as etiologic agents. The portal of entry is considered by some to be the faucial or pharyngeal tonsils, by others the gum margins, and by still others the gastro-intestinal tract. Neither the organism causing the disease nor its portal of entry has been proved.

4 Several well defined epidemics have been reported from various countries in the temperate zones

5 The pathology has not been sufficiently studied. Descriptions of excised glands are given by Spiunt and Evans, Longcope, Downey and McKinlay and in our own cases

6 The symptomatology is similar to that of other acute infectious diseases, with the additional symptoms caused by enlarged tender glands, either superficial or between the muscle layers of the neck

7 The physical conditions are largely confined to the fixed lymphatic tissue

8 The modes of onset, because of their great variability, embody one of the chief difficulties in diagnosis

9 The total leukocyte counts are usually above normal at the onset and below normal during convalescence. A polymorphonuclear leuko-

cytosis may occur at the onset, especially in cases with marked febrile reactions. Sometime during the course the blood shows a rather marked increase in abnormal mononuclear cells. Many of these abnormal cells are lymphoid in nature but some are no doubt endothelial leukocytes or monocytes. Occasionally the monocytes may outnumber the lymphoid cells. There often is an almost complete lack of normal small lymphocytes in the blood stream.

10 The occurrence of a relative or absolute lymphocytosis with abnormal lymphoid cells in the blood stream is significant only of acute lymphoid hyperplasia and is in no way limited to, nor specific for glandular fever, nor does the percentage of these abnormal cells bear any direct relation to the amount of demonstrable glandular enlargement.

11 The diagnosis of glandular fever is often difficult because no specific test exists, because the disease may so closely resemble other acute infections, because of its bizarre manifestations and because so many very mild cases are met with.

12 The question of disease entity must remain open.

13 The best name for the condition would seem to be glandular fever (infectious mononucleosis).

LIPOID NEPHROSIS *

FRANCIS D MURPHY, M D
AND
LOUIS M WARFIELD, M D
MILWAUKEE

That there is still far from unanimity of opinion in regard to the degenerations and inflammations of the kidney is evident from a perusal of the literature. No classification is perfectly satisfactory, but Addis¹ has given us to date one of the most workable of all the clinical classifications. Also the interpretation among writers of any complicated kidney disturbance is far from being uniform. This state of affairs is not recent. It was this uncertainty and foggy conception of the kidney diseases which led von Mueller² in 1905 to separate the apparently degenerative from the evidently inflammatory lesions. His terminology, nephrosis and nephritis, has not passed into current medical terminology without criticism from many quarters, chiefly among his own German colleagues, Aschoff,³ Lohlein⁴ and others, but gradually it has gained in favor until, now popularized by Volhard and Fahr,⁵ Lichtwitz,⁶ Munk⁷ and others, it evidently has come to stay.

There are good grounds for this distinction. Many febrile diseases, many poisons, certain unknown factors all nonproductive and non-inflammatory, cause definite changes in the tubular epithelium of the kidney which are temporary. The lesions are purely degenerative and even if of necrosing character, as after mercuric chloride poisoning, the tubular epithelium regenerates promptly. One may say in general that inflammatory processes affect glomeruli primarily and the tubules secondarily, while degenerative processes affect the tubules primarily and the glomeruli secondarily. The confusion arises when one is engrafted on the other. Frandsen⁸ on the basis of his experiments questions the propriety of separating the nephroses from the nephritides as Volhard has done. Frandsen found that by injecting the veins of

* Presented before the meeting of the Association of American Physicians, Atlantic City, May, 1926.

1 Addis, T. Clinical Classification of Bright's Disease, J A M A **85** 163 (July 18) 1925.

2 Von Mueller. Verhandl d deutsch path Gesellsch, Meran, 1905.

3 Aschoff, quoted by Kaufmann, Spezielle pathologische Anatomie, Berlin, 1922, p 1030.

4 Lohlein. Deutsche med Wchnschr, no 43, 1919.

5 Volhard and Fahr. Die Brightsche Nierenkrankheit, Berlin, 1914.

6 Lichtwitz. Berl klin Wchnschr, 1917, p 1233.

7 Munk, F. Die Nephrosen, Med Klin, nos 39-41, 1916.

8 Frandsen. Studies on Chronic Artificial Nephritis, Skandin Arch f Physiol **46** 193, 1925.

rabbits with repeated doses of potassium bichromate at suitable intervals at first only the tubules were affected. Later there were interstitial changes, round cell infiltration and fibrosis, and still later glomeruli were affected. The resulting picture was a nephrosclerosis.

That pure types of each occur can no longer be a matter of dispute. The discussion is now centering on a type of chronic nephrosis called by Volhard⁸ "genuine," by Munk⁹ "lipoid," by Epstein¹⁰ "chronic nephrosis."

Munk classifies the nephroses under a number of types, all of which he considers to be degenerations:

- 1 Albuminous degeneration

- 2 Fatty degeneration

- 3 Lipoid degeneration

- 4 Necrotic degeneration

- 5 Hyaline degeneration

- 6 Amyloid degeneration

- 7 Vacuolar degeneration

- 8 Glycogen degeneration of the collecting tubule epithelium in diabetes mellitus

Years ago Delafield and Prudden¹¹ divided the affections of the kidneys into degenerative, productive and proliferative. They called attention at that time to the fact that all febrile albuminurias, with the exception of that due to scarlet fever and occasionally to other acute infectious diseases, were not inflammations but were degenerations of the convoluted tubular epithelium. The productive and proliferative changes were the result of inflammatory processes.

The disease that used to be called chronic parenchymatous nephritis with large white kidney is quite probably the disease that is now called chronic nephrosis. Epstein¹² among others published cases and discussed fully their importance. He called attention to a disease in which there seemed to be a disturbance of metabolism with edema and scanty urine output as the outstanding symptoms. The important signs were albuminuria, at times reaching enormous figures, 50 Gm daily, hypercholesterinemia, reversal of the albumin-globulin ratio in the blood serum, and diminution in the total plasma proteins. There were no changes in the circulatory system, no increased nonprotein nitrogen in the blood. Kidney function was low and nitrogen was excreted but sodium chloride was retained. Epstein has reported a number of cases of this general type and has proposed the name diabetes albuminurica for them. The etiology is quite unknown. It attacks young people,

9 Munk, F. *Nieren-Erkrankungen*, Berlin, 1925.

10 Epstein, A. A. *Am J M Sc* **163** 167 (Feb.) 1922.

11 Delafield and Prudden. *Text Book of Pathology*.

12 Epstein, A. A. *M Clin N Amer* **4** 145 (July) 1920.

runs a variable, at times very long course, and tends toward recovery provided no intercurrent infection carries the patient off or no infection damages the kidneys. We have seen no report of Epstein of a fatal case.

Under the term lipid nephrosis Munk⁹ describes a disease with the following chief characteristics. It occurs in young people, coming on slowly and insidiously without known cause. The first symptom usually is edema. There are headache, lassitude and loss of appetite. The urine is scanty as a rule. On examination there is extreme albuminuria with casts but no red blood cells. The concentration of the kidney for nitrogen is normal. Function is decreased. The blood pressure is not elevated. There is hypercholesterinemia, often macroscopically milky serum, there are no eye-ground changes. In the urine sediment are anisotropic (doubly refracting) lipid crystals. The course of the moderately severe case lasts for months, there is a remarkable cyclic character to the edema which is not apparently influenced by any method of treatment and the patients tend toward recovery often with a little albumin in the urine for many months. There is a tendency to chronicity in some with the production of a nephrotic contracted kidney. On the whole, however, the condition can be looked on as a benign one in contrast to the inflammatory lesions producing glomerulonephritis. The pure type seems to be uncommon although the literature now contains a number of cases. Volhard, Fahr⁵ and Munk⁹ have reported cases in their monographs. Karger and Ullmann,¹³ Kaufmann and Mason¹⁴ (two cases, their type I and type III), Beumer,¹⁵ Major and Helwig,¹⁶ Mason¹⁷ and Epstein¹⁰ have reported cases that apparently conform to this type although Munk is the first author who has definitely called attention to the presence of the doubly refracting lipoids in the urine and in the tubules and interstitial tissue of the kidneys. Major and Helwig speak of finding a few of these lipoids in their case. The cases reported by Rabinowitch and Childs,¹⁸ and Peters, Bulger and associates¹⁹ (except their case 2) do not seem to be pure cases of nephrosis. They appear to be cases of glomerulonephritis to which nephrosis was added as a complication.

13 Karger and Ullmann. *Klin Wchnschr* **4** 502 (March 12) 1925.

14 Kaufmann, J., and Mason, E. Nephrosis. Clinical and Pathologic Study, *Arch Int Med* **35** 561 (May) 1925.

15 Beumer. *Arch f Kinderh* **68** 105, 1921.

16 Major, R. H., and Helwig, F. C. *Bull Johns Hopkins Hosp* **36** 260 (April) 1925.

17 Mason, E. H. *Internat Clin* **1** 163 (March) 1926.

18 Rabinowitch, I. M., and Childs, M. C. C. Contribution to Biochemistry and Treatment of Chronic Nephrosis (Epstein), *Arch Int Med* **32** 758 (Nov) 1923.

19 Peters, J. P., and Bulger, H. A. Relation of Albuminuria to Protein Requirement in Nephritis, *Arch Int Med* **37** 153 (Feb) 1926.

Considerable difficulty arises at times in differentiating cases of nephrosis from cases of glomerulonephritis seen during the stage when edema is still present and when the blood pressure is not elevated. The conception of Munk and others is that the tubules never are attacked by inflammation primarily at least. When tubular changes occur in the course of a glomerulonephritis they are degenerative in character and either are dependent on the original inflammation or are the result of some generalized metabolic disturbance which throws on the kidney tubular epithelium foreign substance which must be excreted and which damage the epithelium during their excretion.

Again, in the cases of pure nephrosis infection may be engrafted so that one sees nephritis with nephrosis and nephrosis with nephritis. When a case of glomerulonephritis with blood cells in the urine shows edema and marked albuminuria then nephrosis is superimposed. On the contrary when blood cells are found in a case thought to be nephrosis and the blood pressure rises then nephritis has been added. If one holds to this conception it simplifies to some extent the chaos into which kidney disease has been brought.²⁰

Cases of pure lipid nephrosis reported in the literature are so uncommon that a case studied by one of us (F. D. M.) from the beginning of illness to death with numerous observations covering a period of more than a year should be of importance in clarifying our conceptions of the process in spite of the fact that we know so little about the conditions that lead to the peculiar disturbance of metabolism concerned in the production of the disease.

REPORT OF CASES

CASE 1—A young white man, aged 21, a mechanic, was admitted to the Milwaukee County Hospital, Oct. 27, 1924, complaining of swelling of the legs and headache which had been present for the last three weeks. In his past history there were only scarlet fever, which he had passed through at the age of 10, and gonorrhea at 20.

On physical examination he was well built and well nourished with some pallor. There was considerable edema of the legs and the face and eyelids were quite puffy. The lungs were clear. There were no murmurs in the heart. There was no dyspnea. The blood pressure was 118 systolic, 70 diastolic. The blood vessels were soft. The abdomen was soft. No masses were felt and no fluid was made out. The reflexes were all present and normal. On examination of the urine there was considerable albumin found and under the polarizing microscope there were many doubly refracting lipoids. There were no red blood cells and very few hyaline casts and a few pus cells. The phenolsulphonphthalein test revealed 60 per cent excretion in two hours. Blood examination revealed a normal cell count. When the blood was drawn for chemical examination it was noted that the serum was distinctly milky. The cholesterol content was 500 mg. per cent. The Wassermann reaction was negative. There were no changes in the eve-

²⁰ This leaves out the question of the kidney of pregnancy which is generally looked on as a nephrosis but which is also at times accompanied by increased blood pressure. The changes in the kidney are intimately bound up with a disturbance of metabolism. There is not actual kidney disease (Kollert).

grounds. While he was under observation several basal metabolic rates were made which ranged between -10 and -15 . On account of technical difficulties the albumin-globulin ratio was not determined.

During his stay in the hospital he was at first placed on the ordinary nephritic treatment, low protein and salt free diet with limited fluids. Diuretics such as calcium chloride and novasurol were given from time to time, but seemed to have no influence on the edema. The high protein diet as recommended by Epstein was attempted but he was unable to eat the diet and no beneficial results were evident. During the eighteen months that he was in the hospital, the edema reached such

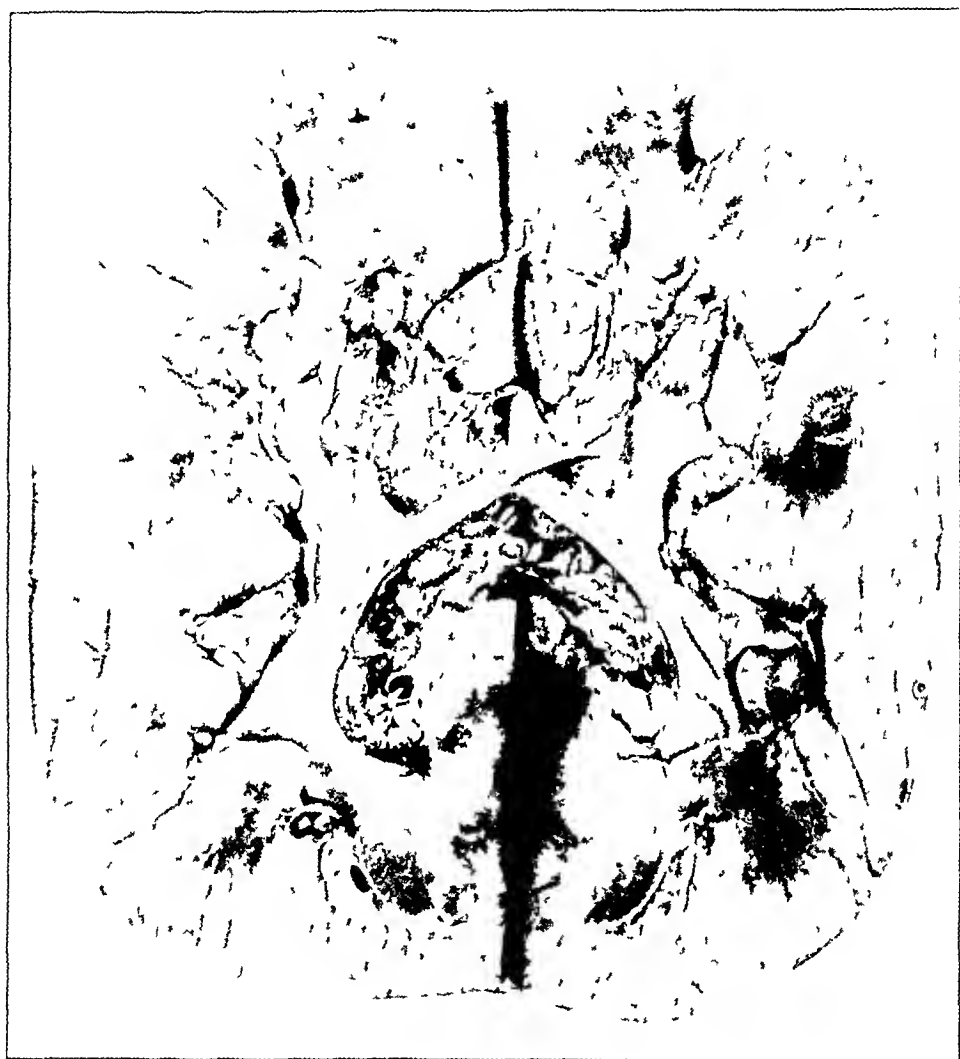


Fig 1—Right kidney, showing increased thickness of cortex and general pallor of organ

a degree on several occasions that the skin over the legs and abdomen cracked and he lay in a semicomatose condition for days at a time. However, during these periods neither the blood nonprotein nitrogen nor the blood pressure showed any changes. For no apparent reason the edema would then disappear and he would then get out of bed and seem to be in reasonably good condition except for the constant albuminuria. These periods of fluctuation of the edema seemed to have no relation to diet or treatment.

Dec 1, 1925, he was placed on rather large doses of thyroid extract which seemed to have some effect in prolonging the intervals between the attacks of edema, and for several weeks the cholesterol in the blood showed a slight decrease. It always, however, remained well above normal values.

In spite of the thyroid treatment he again had an attack of edema the first week in February, which reached an extreme degree. He became comatose again and, February 19, following several convulsive seizures he died. During this last attack of edema neither the blood urea nitrogen nor creatinine became elevated but the cholesterol of the blood advanced from 300 to 700 mg per cent.

We were permitted to do only a partial necropsy. This was performed by Dr W Thalheimer whose report is as follows:

The body was that of a well nourished young man, showing marked edema of the legs, face and eyelids and slight edema of the scrotum. The body was still warm and showed no rigor mortis, but there was slight postmortem discoloration.

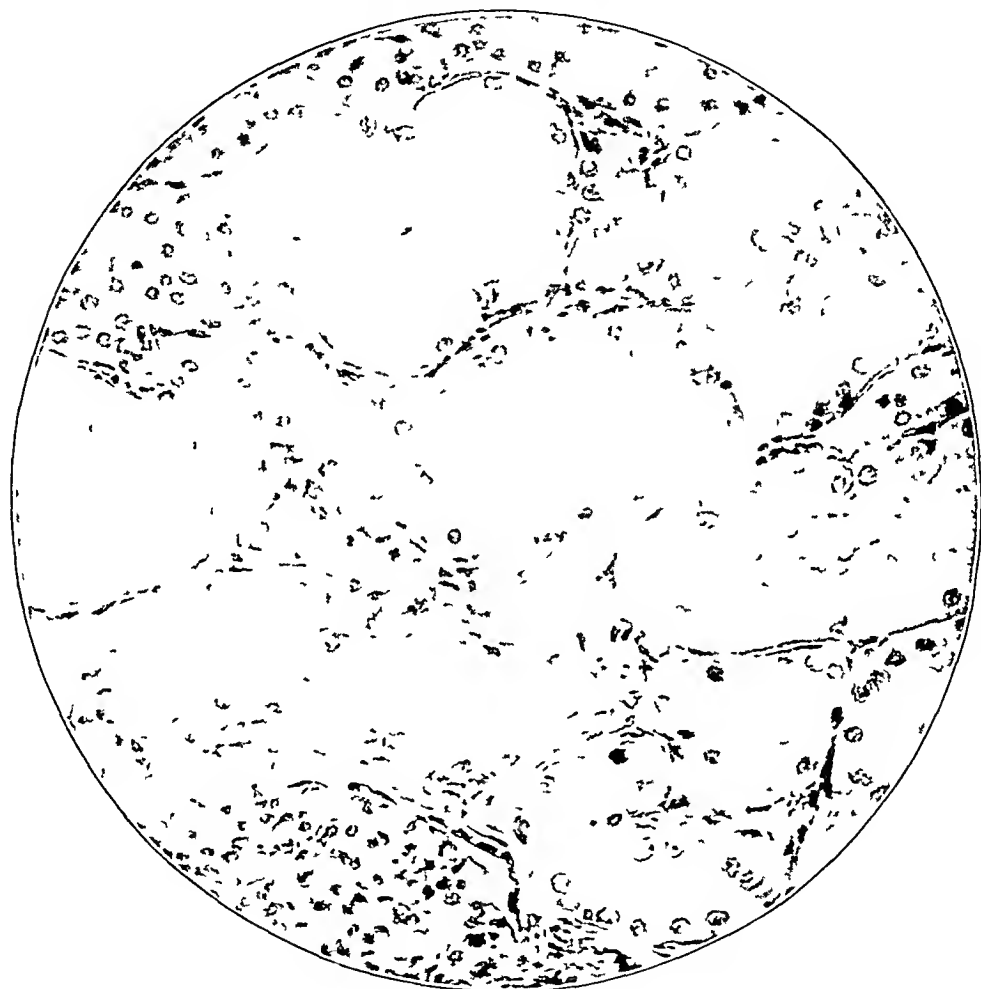


Fig 2—Area showing swollen convoluted tubule cells, many having undergone necrosis, with granular detritus in the lumina, $\times 800$

The peritoneal cavity was opened through a small incision. Both layers of the peritoneum were smooth and glistening and there was a small amount of clear yellow fluid free in the cavity. The tissues of the abdominal wall and the tissues in general were slightly edematous. The kidneys were large, firm, pale and were similar in appearance. The left weighed 220 Gm, the right, 195 Gm. The capsule stripped with difficulty, splitting here and there, leaving, however, when completely stripped a perfectly smooth surface. The surface was extremely pale, of a mottled creamy white and pink. On section, the cortex was a peculiar cream white and had a greasy appearance, measured from 12 to 14 mm, and was well marked off from the pyramids. The pelves appeared normal. There was no

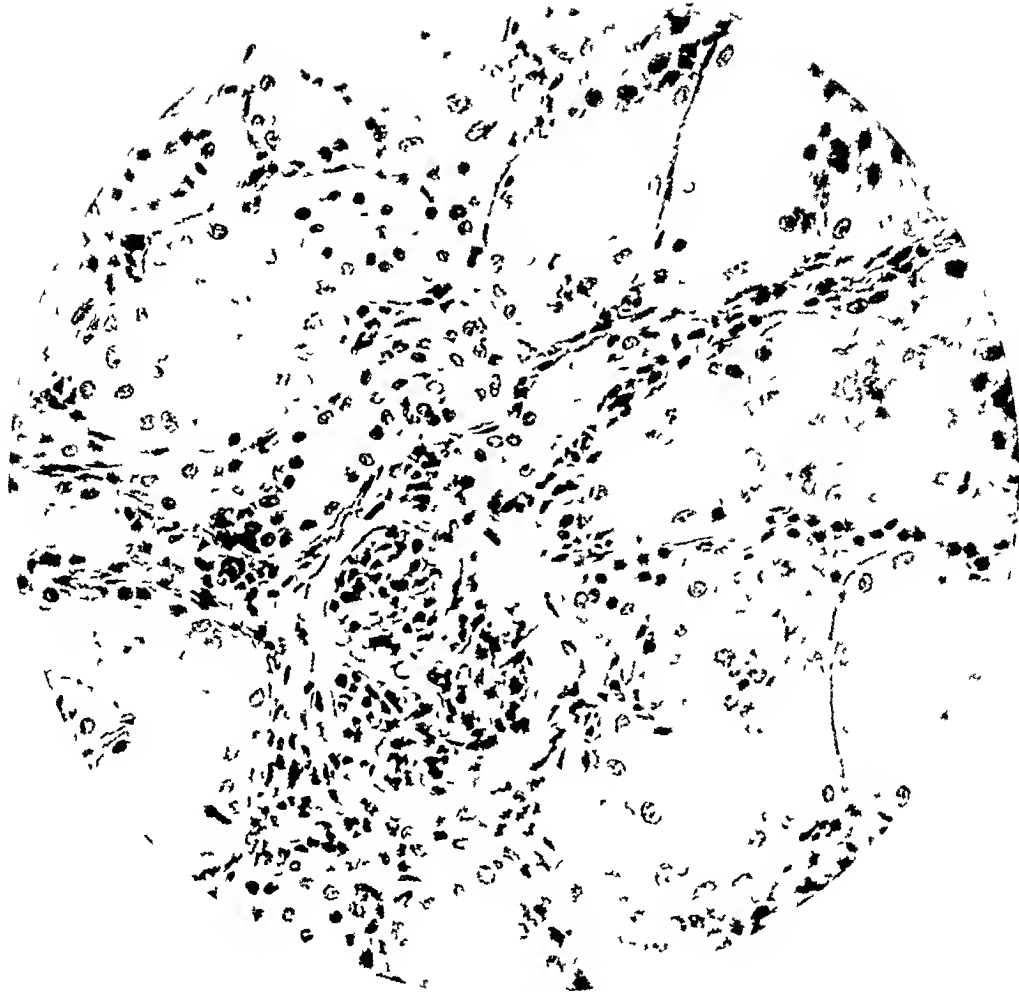


Fig 3—Glomerulus, typical of all seen, revealing no inflammatory lesions, except for edema the glomerulus and capsule are normal, $\times 400$

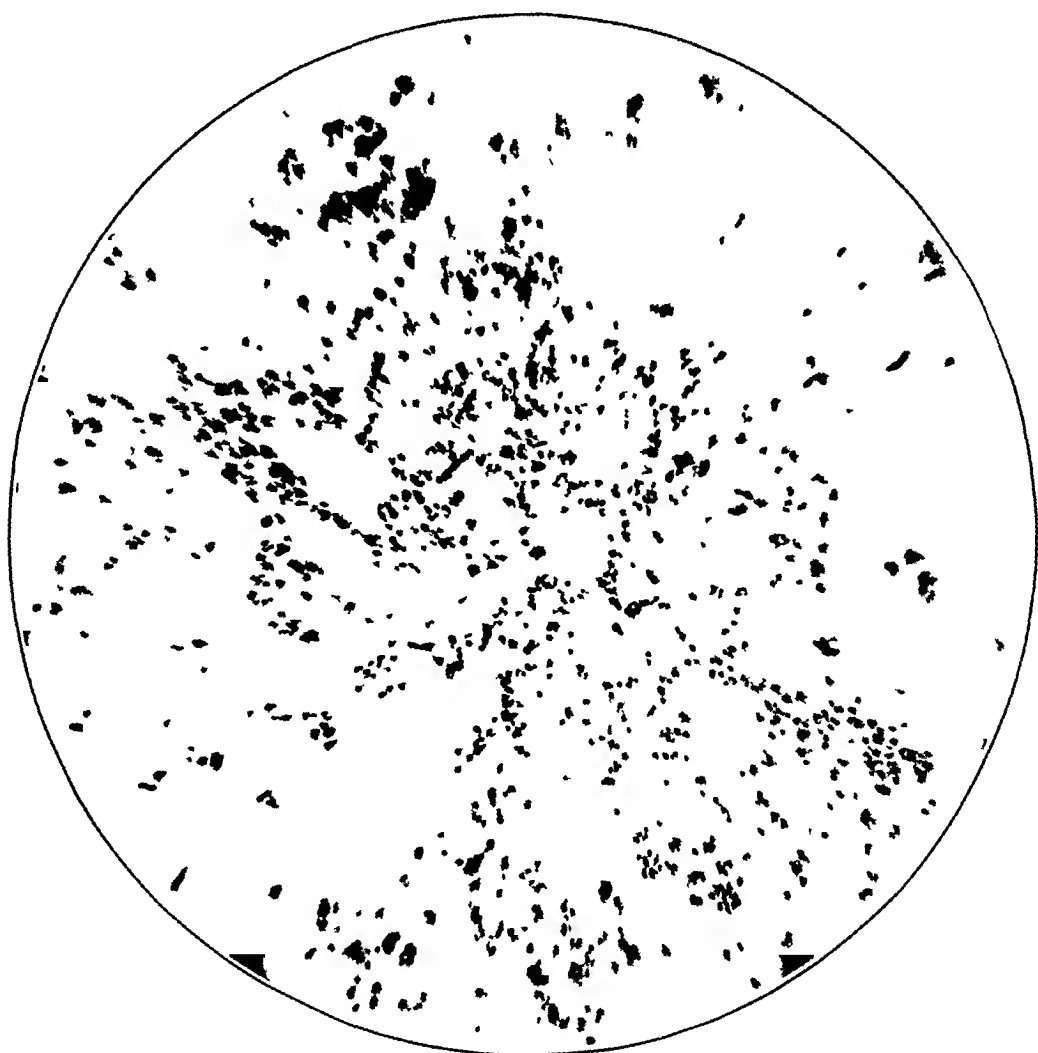


Fig 4—Appearance of fresh section seen with the polarization attachment to the microscope, the doubly refracting bodies are in both the tubule cells and the interstitial tissue, $\times 800$

increase in the fat The suprarenals appeared normal The spleen was normal The liver was normal in size On section it was pale and edematous and showed a moderate congestion The heart was normal in size and shape The pericardium was smooth On opening the heart in the aortic leaflet of the mitral valve there was a slightly raised yellowish area Similar deposits were found in the aortic cusps and in the intima at the root of the aorta The abdominal aorta showed numerous yellowish irregular elongated areas slightly raised above the surface as well as small rounded button-like areas

Microscopic examination of the kidneys showed the glomeruli to be normal in appearance, for the most part they completely filled the spaces but nowhere were there any signs of acute or chronic inflammatory changes The capillary loops were everywhere normal in appearance, and showed no thickening or increase of

TABLE 1—Detailed Data of Case 1

Date	Blood			Function Tests			Urine				Basal Metabolic Rate	Treatment
	Blood Pressure		Urea Nitrogen	Cholesterol	Phenolphthalein	Urea Coefficient	In take	Output	Albumin	Doubly Refracting Lipoids		
	Systolic	Diastolic										
10/24/24	110	60	22		50	54.0	1,200	850	III		Diuretics	
11/25/24	120	70	20		60		1,200	650	III			
12/26/24	116	70	12		70		800	40	III			
1/23/25	110	70	18		55		1,200	2,000	III	Present	Novasurrol blood transfusion	
2/28/25	115	78	14		60		1,200	50	III	Present		
6/7/25	110	60	15		65	66.6	800	250		Present		
8/3/25	125	70	19		60		1,000	300	III	Present	—15 —10 —15	
9/29/25	115	70	24		75	55.0	1,200	1,075	III			
12/1/25				806			1,200	1,000	III			
12/11/25				659	65		1,200	1,100	III	Present	Thyroid extract, 20 grains (13 Gm) three times a day	
12/21/25	120	75		630			1,400	900	III			
1/4/26			14	451	60		1,500	1,150	III	Present		Thyroid extract, 20 grains (13 Gm) three times a day
1/18/26			12	481			1,200	800	III	Present	Thyroid extract, 20 grains (13 Gm) three times a day	
1/25/26	115	65	9	721	70	52.7	1,200	1,500	III	Present		
2/1/26	110	65		555			1,100	600	III			Thyroid extract, 20 grains (13 Gm) three times a day
2/10/26	120	70	16.8		60		1,000	250	III	Present	Thyroid extract, 20 grains (13 Gm) three times a day	
2/15/26	125	65			55		900	100	I			
2/18/26	112	65		695			600	50	III			Thyroid extract, 20 grains (13 Gm) three times a day

cellular content On the other hand, proximal convoluted tubules revealed extensive and profound degenerative changes The cells were pale and swollen The nuclei were often not visible The protoplasm had a granular appearance The lumina of the tubules were filled with granular debris The tubular cells showed a uniform stain with sudan III Examination with polarized light revealed doubly refracting lipoids both in the cells and in the interstitial tissue This lipid material was insoluble in alcohol The collecting tubules showed no definite changes and there was no evident lesion in the small arteries The heart muscle showed only a slight cloudy swelling, otherwise there was no noticeable change Sections of the aorta through one of the yellow patches showed characteristic lesions of atheroma in the intima The staining of the intimal thickening with sudan III was quite heavy but the material was dissolved out in alcohol No doubly refracting bodies were found in the intimal atheromatous patches The liver spleen and suprarenal showed no particular change

CASE 2—A young white woman, aged 25, a stenographer, began to have headaches and puffiness of the ankles and face especially around the eyes during the spring of 1921. She consulted a physician at that time, who found a marked albuminuria with some pus cells and casts but no red blood cells. The blood pressure was normal. No kidney function tests and no chemical blood analysis were made. She came under the observation of one of us (F D M) Nov 7, 1922, complaining of headache and puffiness of the eyes and ankles. She reported that at times during the last year and one-half the dropsy and headache had disappeared for periods varying from one to three months. The urine at this time showed a moderate quantity of albumin with pus cells but no red blood cells and

TABLE 2—Detailed Data of Case 2

Date	Blood				Func- tion Phenol sulphon phthal- cin	Urine				Treatment	Remarks
	Blood Pressure		Urea Nitro- gen	Chol- es- terol		Albu- min	Doubly Re- fracting Lipoids	Casts			
	Sys- tole	Dias- tole									
11/ 7/22	120	80	11.8		65	III pus cells		Hyalin	Low protein, salt free diet	Edema, slight	
12/ 5/22	118	80	16		70	III pus cells		Hyalin	Low protein, salt free diet	Edema slight	
2/14/23	112	60				III pus cells		Hyalin	Low protein, salt free diet	Edema, slight	
4/ 3/23	128	80	20			III pus cells			Low protein, salt free diet	Edema	
5/21/23	115	80				III			Low protein, salt free diet	No edema	
8/16/23	125	75				III			Diuretics	Edema	
10/ 3/23	115	75	18			III pus cells		Hyalin	Diuretics	No edema	
12/18/23	126	80				III		Pus cells	Diuretics	No edema	
2/17/24	118	65	12			III			Diuretics	Edema, head- ache	
4/ 6/24	112	75	16			III		None		Edema, head- ache	
9/ 1/24	125	75				I	Present	Few hyalin		Edema, slight	
11/21/24	115	70	10			I				Edema	
2/19/25	110	60				II	Present			Edema	
6/23/25	116	75		226		III	Present			Edema, slight	
8/12/25	120	70		324		II		Pus cells	High protein, low fat diet Thyroid extract, 15 grains (0.9 Gm) three times a day	No edema	
10/ 7/25	124	65	15	388	60	III	Present	Pus cells	Thyroid extract, 15 grains (0.9 Gm) three times a day	Edema, slight	
12/ 5/25	116	75		284	75	III	Present	Pus cells	Thyroid extract, 15 grains (0.9 Gm) three times a day	Edema, slight	
12/12/25	122	80	18	312	55	III	Present	Pus cells	Thyroid extract, 15 grains (0.9 Gm) three times a day	Edema, slight	
12/22/25	110	70				III	Present	Pus cells	Thyroid extract, 15 grains (0.9 Gm) three times a day	Edema, slight	

no granular casts were seen. The blood pressure was 128 systolic, 80 diastolic, the phenolsulphonphthalein showed 65 per cent in two hours. The blood urea nitrogen was 16.8 mg per hundred cubic centimeters. The Wassermann reaction was negative. The blood count and differential count were normal. She was placed on a limited fluid intake and limited protein diet to about 50 Gm a day. The headache was treated symptomatically, and she continued to work. During 1923 and 1924 she was seen at intervals of one and two months and very little change occurred during this period except for the slight fluctuation in the amount of the albumin in the urine. The urea nitrogen of the blood ranged between 14 and 20 mg per hundred cubic centimeters and the phenolsulphonphthalein tests always gave high figures. The edema and headaches came and went together but neither ever became marked enough to cause her to give up her work, except on two occasions when she missed her office work two days each time.

About Jan 1, 1925, the urine was examined for the presence of doubly refracting lipoids. They were found on many occasions. The blood cholesterol was increased, varying from 266 to 388 mg per hundred cubic centimeters. The treatment was then changed to high protein low fat diet. The change, however, was not carried out by her as she had been told that meat and eggs were harmful and she did not eat the high protein diet. She did, however, take about 70 Gm of protein a day for a while and thought that she felt worse. The edema, which was slight at that time, was not influenced by any change in the diet. During December, 1925, she was given thyroid extract with no apparent result. She took it for a while but as she felt rather well and could see no object in taking the medicine, she discontinued the treatment.

CASE 3—A young white man, aged 24, a clerk, was seen first by one of us (F D M) Dec 9, 1925, complaining of swollen ankles and face, with headache and loss of appetite. Except for a gonorrheal infection at 18 he had never been

TABLE 3—Detailed Data of Case 3

Date	Blood				Function Tests			Urine			Treatment
	Blood Pressure		Urea Nitrogen	Cholesterol	Phenol sulphthal ein	Urea Coefficient Factor	Output	Albumin	Doubly Refracting Lipoids	Basal Metabolic Rate	
	Systolic	Diastolic									
12/ 9/25	125	75	18	666.6	60	58	300	III	Present		Thyroid extract, 18 grains (11 Gm.) three times a day
12/15/25	125	80	12	500	70	60	600	IIII	Present	+10	Thyroid extract, 18 grains (11 Gm.) three times a day
12/28/25	120	70		512	65		1,000	III	Present	+15	Thyroid extract, 18 grains (11 Gm.) three times a day
1/ 8/26	116	70	14	454	55	70	2,000	III	Present	+10	Thyroid extract, 18 grains (11 Gm.) three times a day
1/15/26	125	65	12			65	1,300	IIII			
1/19/26	130	80		374	75		1,000	III	Present		Thyroid extract, 18 grains (11 Gm.) three times a day
2/ 1/26	125	75	18	340			1,500	III	Present		Pneumonia treatment
2/ 5, 26	110	60	16				1,400	III	Present		Pneumonia treatment
2/ 9/26	118	70					1,600	III	Present		Pneumonia treatment
2/15/26	115	70	14	275	64	71	1,500	III			Thyroid extract, 15 grains (0.9 Gm.) three times a day
2/18/26	120	80					1,200	III			Thyroid extract, 15 grains (0.9 Gm.) three times a day
3/ 1/26	115	80	20	88			1,400	III			Thyroid extract, 15 grains (0.9 Gm.) three times a day

ill. His present trouble dated from some time in October, 1925, and came on without any cause so far as he could think of. After some treatment at that time the symptoms subsided for a month, when they slowly returned.

On examination there was considerable edema of the legs and face. The heart, lungs and abdomen were normal. The blood pressure was normal and the Wassermann reaction was negative. Urinalysis showed albumin with doubly refracting lipoids but no red blood cells. On withdrawing the blood for chemical analysis a thick layer of creamy material came to the surface. The cholesterol was 666.6 mg per hundred cubic centimeters. The urea nitrogen was not elevated. Kidney function tests revealed no evidence of insufficiency. The basal metabolic rate on several occasions averaged +10. The eye-grounds were normal. The blood pressure was normal on several examinations.

He was placed on a high protein low fat diet and kept in bed for a few weeks, following which the edema disappeared and he felt quite well again. However, after about twelve days the edema returned and he went back to the hospital.

During the stay in the hospital high protein low fat diet with 25 grains (16 Gm) of thyroid extract three times a day were given. This seemed to relieve his symptoms but the urine showed albumin constantly. When he had again recovered to a point where he could leave the hospital he developed lobar pneumonia and made an uneventful recovery. During the course of the pneumonia the edema subsided. Following his convalescence the edema again returned. The cholesterol was 588 mg per hundred cubic centimeters. The urine showed large quantities of albumin and many doubly refracting lipoids. During this attack he became discouraged and thought that he would seek the services of another physician. He has not been seen since.

CASE 4—This patient was not observed by either one of us but the urine was sent for examination and the history was later obtained.

A young white woman, aged 20, a member of a religious order living in Canada, began to have swollen ankles and puffiness of the hands and face in July, 1925. The family and past histories were negative. The urinalysis at the time of her first illness showed considerable albumin but no red cells and no granular casts. There were numerous doubly refracting lipoids. The blood pressure was normal as well as the urea nitrogen of the blood. The phenolsulphonphthalein excretion on several occasions was between 50 and 60 per cent in two hours. The cholesterol content of the blood was 320 mg. The heart was normal. The eye-grounds were normal. The Wassermann reaction was negative. The basal metabolic rate ranged between +10 and +15.

The blood count revealed 4,600,000 red cells, 6,800 white cells, 75 per cent hemoglobin, with a normal differential count. The edema fluctuated in intensity during all this period but never entirely disappeared. She felt weak most of the time and suffered from headache quite often. The albuminuria was always present.

Feb 12, 1926, she was given high protein low fat diet and 60 grains (3.8 Gm) of thyroid extract daily, after which the edema was less. The albuminuria was not so excessive but it always was present. The general condition was reported as improved and she was able to continue her work.

It is quite impossible to say how frequently lipid nephrosis would be found if all cases with suggestive symptoms and signs were carefully examined for the doubly refractive lipoids. Munk naturally reports most of the cases. Yet he finds them relatively uncommon since the Great War. Epstein²¹ says that the type described by him is common enough for him to be able to show several patients in his wards at any time. Eppinger²² says that in two years he had not had a case of pure nephrosis in his service at the First Medical Clinic in Vienna. A rather thorough search through the literature reveals the fact that little attention is paid by the English speaking men to the point that Munk considers so characteristic.

The following reports on nephrosis have been found in the English and American literature. Kahn²³ reports on cases of chronic parenchymatous nephritis. His cases, however, do not conform to Epstein's

²¹ Epstein, A. A. Personal communication to the authors.

²² Eppinger. Personal communication to the authors.

²³ Kahn, M. Protein and Lipin Content of Blood Serum in Nephritides, *Arch Int Med* 25 112 (Jan) 1920.

cases or to Munk's cases Rabinowitch and Childs¹⁸ report a case with systolic blood pressure of 210 mm Their case is evidently (and they admit that it does not represent the pure form) one of chronic glomerular nephritis plus nephrosis There was a low plasma protein with reversal of the albumin-globulin ratio and high cholesterol (up to 781 mg per cent) A high protein diet in spite of the nonprotein nitrogen retention did not increase the concentration of nonprotein nitrogen This is unusual, the opposite usually occurs

Major and Helwig¹⁶ report a case that seems to conform to the type we are here describing but with certain differences in the pathologic picture in the kidney They found some of the glomeruli showing engorgement with red blood cells The glomeruli showed a mild degree of acute glomerulitis They found only an occasional anisotropic lipid crystal with the polarizing microscope There were patchy areas of fibrosis throughout the interstitial tissue The whole course of their patient's illness was about nine months We surmise that in view of the observations in the glomeruli that an acute nephritis was superimposed on chronic nephrosis Peters and Bulger¹⁹ report an interesting study on the relation of albuminuria to protein requirement in nephritis and report six cases However, only one of the cases, their case 3, as they readily admit, could be admitted into the group of true chronic nephrosis

Kaufmann and Mason¹⁴ report three cases that they consider represent three types Their case 1, type 1, appears to be pure nephrosis Their case 2, type 2, seems to be secondary contracted kidney with superimposed nephrosis Their case 3, type 3, is also nephrosis, which in course of time produced some changes in the glomeruli and interstitial tissue which Munk, Kollert²⁴ and others do not look on as inflammations Their first patient died of pneumococcus peritonitis This is interesting Volhard²⁵ reports four cases of pure nephrosis, Munk⁹ one case of his lipid nephrosis in which septicemia of low grade, yet fatal, was due to the pneumococcus

Dyke²⁶ reports on the pathology of nephritis associated with edema He studied six cases in all of which were edema, albuminuria and cylindruria Histologically there were degeneration of the epithelium of the renal tubules and deposition in degenerated renal tubular epithelium of large quantities of doubly refracting lipid material However, it seems to us, after a critical study of his data, that only case 103, the boy aged 8 years, could be classed as pure nephrosis Four of the patients were in the fifties with increased blood pressure and one had an amyloid kidney

24 Kollert V *Ztschr f klin Med* **97** 287 (Sept.) 1923

25 Volhard *Deutsche med Wchnschr* no 15, 1918

26 Dyke, S C *Quart J Med* **18** 77 (Oct.) 1924

Mason¹⁷ records an important case under his observation for thirty months, from the time of onset to death. The cause of death was acute miliary tuberculosis. This case showed all the essential features of lipoid nephrosis except that no mention is made of the anisotropic lipoids in the urine during life or in the kidney after death. The kidneys showed a typical nephrotic contracted kidney without signs of inflammation. Munk says in this connection (page 295), "On the other hand, accidental inflammatory and sclerotic processes may well occur in later life in the kidneys of every case of chronic nephrosis, so that the pathogenesis of the histologic finding before us can no longer anatomically be decided with certainty." Munk agrees with Volhard and Fahr, who believe that there is such an end-stage as a nephrotic contracted kidney. This case so carefully studied by Mason lends support to this opinion.

There is one other interesting fact connected with this case: there was no definite relation between the total plasma protein or the albumin-globulin ratio and the degree of the edema. Further, the high protein diet was not followed by improvement.

Rigler and Rypins²⁷ report three cases which apparently belong to this group of cases. One patient was a young woman, aged 21, one was a man, aged 34, and one was a child, aged 2½ years. The young woman was living when she was heard from last, the man was reported to have died, the child died. Postmortem examination of the child revealed large pale kidneys. No microscopic report was given. The clinical signs and laboratory examinations corresponded to Epstein's chronic nephrosis. There was no examination for double refracting lipoids.

Conrad²⁸ publishes a purely clinical report of a woman aged 40. Although this patient was beyond the age usually found in cases of primary nephrosis and although there were no laboratory examinations except routine urinalyses given, yet the other characteristic symptoms and signs were present. The patient improved when placed on Epstein's high protein low fat diet. This case is included in spite of the lack of both chemical examination of the blood and microscopic examination of the urine for anisotropic lipoids.

THE EDEMA

It would lead us too far afield to discuss the question of the genesis of edema. It must suffice to give briefly the opinions of several authors who have been especially interested in this particular edema which is characteristic of chronic nephrosis.

27 Rigler, L. G., and Rypins, H. *Minnesota Med* 7 419 (June) 1924.

28 Conrad, C. E. *Virginia M. Monthly* 48 375 (Oct.) 1921.

There is agreement that it is extrarenal in origin and that it is connected intimately with the colloids. Epstein¹⁰ thinks that due to the unexplained metabolic change, which causes enormous losses of protein through the urine, and the decrease in the plasma proteins that the osmotic balance between the blood and tissues is disturbed and fluid collects in the tissues. The fluid is poor in protein but contains the blood salts and urea.

Both Munk⁹ and Kollert²⁹ explain the edema in much the same way, except that they draw on physical chemistry more. According to Munk (page 306), there are two kinds of colloids in blood which in respect to their physicochemical relation to water are called lyophil or hydrophil, lyophobe or hydrophobe. The euglobulin fraction, which is increased in the disease under discussion, belongs to the latter group, the albumin fraction belongs to the former, while the pseudoglobulin fraction occupies a middle position. Under normal conditions the dispersion of these colloids is so arranged that an optimal water exchange from serum to tissues and thereby a resulting diuresis take place. We know that the different albumin bodies are capable of change. Albumin and pseudoglobulin can be converted into euglobulin by change in the ion concentration or by the electric current. This change can also take place in the living body. Such a change does take place in this disease not only in colloids of the body fluids but also in the colloids of the tissues.

Kollert²⁹ explains the edema in a similar manner. To him it is the change from the fine dispersible colloids to the large dispersible colloids with the retention of water in the tissues. He looks on nephrosis as a general metabolic disturbance of all organs which causes increased destruction of albumin. The blood only carries the excess. Fibrinogen in the blood is increased. There is also increased rate of sedimentation of the red blood cells. He believes in the extrarenal origin of the edema. His conception of nephrosis, however, differs somewhat from that of Munk. Kollert believes there is at first an infection or intoxication that produces long standing injury to all cells, including the kidney. Now when such an organism is attacked by a kidney disease, be it ever so light, this is added to the already existing tubular damage and the nephrotic symptom complex becomes evident. The kidney lesion which tips the scales, so to speak, is a glomerulonephritis. He admits the possibility of a pure degenerative tubular lesion but considers it most uncommon.

In a recent book on nephritis, Elwyn³⁰ devotes a chapter to the discussion of lipid nephrosis. He quotes no cases of his own. He believes that it is always preceded by glomerulonephritis. The inflammatory

29 Kollert V. Klin. Wchnschr. 5:441, 1926.

30 Elwyn. Nephritis, New York, Macmillan Company, 1926.

changes then subside, the blood pressure returns to normal, but the albuminuria and tendency to edema remain. We cannot agree with this conception for the reasons given above. It is true, as we have already stated, that should such a condition be encountered it would be extremely difficult to differentiate it from pure lipoid nephrosis. That is not the point, however. The fact is that we and others have seen cases in which there were no inflammatory glomerular changes. One cannot get around the facts.

THE NATURE OF LIPOID NEPHROSIS

Pure lipoid nephrosis such as the cases reported in this article arises spontaneously so far as our knowledge goes as an independent disease of obscure etiology (Kollert,²⁹ Munk³⁰). Munk³⁰ states that in his experience syphilis is a cause, and it has followed on long standing pneumococcus sepsis without amyloidosis (Volhard). Secondary lipoid nephrosis is commonly found in cases of chronic glomerular nephritis. It is never found in nephrosclerosis.

Careful comparison of cases reported by Epstein and cases described in a personal interview with him and those described by Munk leaves no doubt in our minds that both are describing the same disease. Certain features are common to the cases described by both, viz., the insidious onset in young people, the absence of etiologic factors, the edema, pallor, albuminuria with few casts and no blood cells, low blood pressure, cyclic character of the edema, hypercholesterinemia, and the generally benign nature of the disease. From these characteristics they diverge. Epstein lays stress on the decrease in the plasma proteins and the reversal of the albumin-globulin ratio. He also more recently emphasizes the decrease in basal metabolism³¹. While Munk says nothing about the albumin-globulin ratio he specifically states that the euglobulin fraction of the serum is increased. He does not mention the lowered basal metabolism. His stress is laid on the presence of the anisotropic lipoids in the urine. He, too, emphasizes the hypercholesterinemia. We feel sure that if Munk had partitioned the plasma proteins he would have confirmed Epstein's observation, and if Epstein had assiduously made use of the polarization microscope he would have confirmed Munk's findings. Both insist that the disease is a metabolic disturbance, Epstein proposing the name diabetes albuminurica.

In a recent review of the subject Kollert²⁹ abstracts briefly all the literature and agrees with those who look on the disease as a primary disturbance of metabolism. The same agent that disturbs the general metabolism of the albumins also injures the kidney tubular epithelium.

31 Epstein, A. A., and Lande, H. Studies on Blood Lipoids. Relation of Cholesterol and Protein Deficiency to Basal Metabolism, *Arch. Int. Med.* **30** 563 (Nov.) 1922.

and the effort on the part of the kidney to excrete the foreign substances further damages the epithelium

It is universally agreed that the protein content of the plasma is low. There is some physical-chemical disturbance in the building of the colloids of the body. One point noted is the increased rapidity of sedimentation of the erythrocytes²⁹

That physical or physical-chemical agents could change serum albumin into euglobulin was shown by Ruppel, Ornstein, Carl and Lasch,³² who passed electric currents through serum albumin. Munk, Benatt and Flockenhaus³³ perfused kidneys of dogs with Ringer's solution. When they passed an electric current through the perfusing fluid before it entered the kidney, albumin was found in the ureteral outflow. They also succeeded in producing an excretion of doubly refracting lipoids by injecting dogs with dog serum diluted with Ringer's solution through which for four hours an 8 volt current had passed. Munk considers that hypercholesterinemia plus lipoidosis of kidney epithelium plus excretion of anisotropic lipoids is a general disturbance of a physical-chemical nature in the body lipoids. In getting rid of these foreign substances the kidneys are damaged and anisotropic lipoids pack the cells of the tubules.

Feeding of enormous amounts of cholesterol does not produce excretion of these lipoids but Gross³⁴ found that by feeding cholesterol to patients who were passing these lipoids in the urine the excretion of them was enormously increased. Genck³⁵ injured the kidneys of a rabbit and a cat with uranium nitrate, then fed them cholesterol, she found not only anisotropic lipoids in the urine but also in the kidneys.

It is characteristic of the cases of lipoid nephrosis that the special lipoids are found in the cells of the interstitial tissue of the kidney. These lipoids have been found in the kidney epithelium of patients with carcinoma in whom there was neither albuminuria or lipoiduria. Some physical-chemical change is postulated in these cases. The anisotropic lipoiduria is not pathognomonic of lipoid nephrosis. However, in a patient who has symptoms and signs enumerated within and in whom these lipoids are found the disease is in the strict sense lipoid nephrosis.

RELATION OF HYPERCHOLESTERINEMIA TO NEPHROSIS

Port³⁶ in 1910 first called attention to the presence of increased cholesterol in the blood in many cases of nephritis. The normal con-

32 Lasch quoted by Munk (footnote 9)

33 Munk, F., Benatt, A., and Flockenhaus, M. *Klin Wchnschr* 4 863 (April 30) 1925

34 Gross, O. *Klin Wchnschr* 2 217 (Jan 29) 1923

35 Genck, Margarete quoted by Munk (footnote 9)

36 Port, quoted by Munk, Benatt and Flockenhaus (footnote 33)

tent ranges between 140 and 170 mg per cent. In a more recent publication Port³⁶ summarizes his results as follows

A marked increase of the cholesterol content of the serum is found in nephroses and in the mixed forms of chronic diffuse glomerulonephritis the more or less marked nephrotic element makes itself known in an increase of the cholesterol picture. On the contrary, the cases of primary contracted kidney show no increase in the cholesterol content. The hypercholesterinemia appears, therefore, as a symptom of the nephrotic element. Benign nephrosclerosis cases show normal values.

Munk does not think that there is any increase in the total cholesterol of the body. There is a redistribution. The cholesterol is brought to the kidney by the blood, esters are formed and these, being foreign substances, damage the kidney epithelium, get in the tubules and are washed into the bladder.

Increased cholesterol content of the serum is an essential feature of lipoid nephrosis whether it is a primary disease, as in the cases described above, or whether the nephrosis is superimposed on chronic glomerulonephritis. An adequate explanation of the hypercholesterinemia is lacking.

COMMENT ON CERTAIN ASPECTS

Every one of the four cases which form the basis of this report have all the distinguishing characteristics that have been laid down by Munk⁹ as those essential to the diagnosis of lipoid nephrosis. These are insidious onset in young persons, excessive edema of a peculiarly fluctuating type, marked albuminuria with or without casts in the urine but without red blood cells, normal blood pressure, and the presence of doubly refracting lipoids in the urine.

These cases seem to belong to a definite and pure type of degenerative kidney disease in which the fundamental process appears to be a metabolic disturbance of the colloids of the body leading to some profound change, in which euglobulin is increased in the blood and cholesterol is passed into the blood stream. Somewhere the cholesterol is changed into esters, reaches the kidney, and there, being a foreign substance, further injures the tubular epithelium.

The difference of opinion is chiefly whether lipoid nephrosis is a pure degeneration or whether as Lohlein and Kollert among others believe, it is produced only as a result of glomerulonephritis. Mason's case cited above seems to prove that the cases can be free from inflammatory lesions for a long time. It was only toward the end of the course that red blood cells and increased nonprotein nitrogen retention were found in his case. Dyke's case 103, mentioned above, is again a pure degenerative lesion. The macroscopic and microscopic description of the large, pale kidneys would fit our case word for word.

Finally, in our case 1 the young man was observed from the beginning of his illness to the end. The cause of death will ever remain

obscure as we could obtain permission to examine the kidneys only. There were no peritonitis and no milary tuberculosis, two diseases that have been responsible for the deaths in the reported cases. Among the striking features in our case were (1) the cyclic character of the edema. It came and went in spite of, and not because of, treatment. This is quite characteristic of all the cases. It would look to a casual observer as if the high protein diet helped. As a matter of fact, the patient could not eat the amount of protein and really did not receive such a large proportion of protein. However, the edema disappeared about that period. (2) The ineffectualness of any treatment with diuretics. A number were tried with no striking effect. (3) The persistence of lack of cardiovascular changes during his whole illness. We are inclined to believe that if he had developed a mild inflammatory lesion of his glomeruli, as happened in Mason's case, there would have been both increased blood pressure and increase of nonprotein nitrogen retention. (4) The independence of the edema of the degree of hypercholesterinemia. This is also found in other cases and does not lend aid to any theory of the explanation of the edema. (5) The absence of all evidence of a glomerular lesion of an inflammatory nature in a case running a course of more than a year and ending in death.

We believe that such a case as our case 1 together with the cases referred to show beyond doubt that there can be a pure degenerative disease of the kidneys affecting the tubules without there being any inflammatory glomerular lesions. This appears to refute the contention of Kollert, Lohlein and others. It is possible to have lipid nephrosis in its pure form. This is primary lipid nephrosis. It appears to be an uncommon disease. However, by making use of the polarization microscope together with the usual chemical and microscopic tests of blood and urine it may well be that such cases will more often be discovered. One of us (F. D. M.) in the last year has found four cases. All conform to a definite type with common symptoms and signs. It may be argued that our criteria are too restricted. However, when in a series of cases there are a number of symptoms and signs all alike, one is justified in stating that such is a definite disease. Were it otherwise we should not have any separation of similar groups of symptoms and signs into various diseases. We do not know the cause. This can be said of many other well defined diseases.

Uremia never occurs in this type of case. Convulsive seizures may occur as in our case 1 and be the precursor of death. The blood pressure does not rise and the nonprotein nitrogen of the blood remains within normal limits. The whole picture differs from that observed in the cases of chronic glomerulonephritis to which nephrosis has been added. Volhard thinks the convulsions are due to edema of the brain. It was unfortunate in our case that we could not examine the head.

Stupor and even coma are not uncommon complications of lipoid nephrosis. They do not necessarily mean a fatal issue in a short time but apparently the prognosis as to eventual recovery is rendered grave.

Our cases 2, 3 and 4 show there is a general tendency to exacerbations and remissions. During the remissions the patients feel quite well and are able to carry on their occupations. The albumin, however, never disappears from the urine. Munk has had patients that he had followed for more than twelve years. They seem well, but have never become albumin-free.

The analogy between these cases and diabetes is striking. Lipoid nephrosis is a disturbance of the metabolism of the proteins and might even be called, as suggested by Epstein, diabetes albuminurica.

A disease in which there is such an increase of cholesterol in the blood would seem theoretically to be helped by a diet poor in fat. This has occurred to others and has been tried with no apparent effect. Epstein,¹⁰ on the basis of the loss of albumin in the urine and the lowered basal metabolism, advises a diet high in protein and low in fat and feeding with thyroid extract. He has given some of his patients huge doses of both thyroxin and of the desiccated thyroid and has noted a remarkable tolerance in patients with chronic nephrosis. Two of our patients received from 60 to 75 grains (3.8 to 4.8 Gm.) of thyroid daily. In one there was no striking benefit, in the other it is too early to say whether benefit will continue.

As a matter of fact all cases do not have low basal metabolic rates. Further, can one say that in a patient whose tissues are edematous and whose weight is therefore a matter of estimation that a -10 or -15 rate means hypothyroidism? We doubt whether that is a justifiable conclusion. Even the patient who has lost his edema is still ill and usually undernourished, so that a rate around -10 or -15 would not be so unusual. Just how to explain the enormous tolerance of some of these patients for thyroid extract is difficult, if not impossible. We shall not make any attempt at explanation.

SUMMARY

In four cases of a kidney affection corresponding to Munk's lipoid nephrosis reported here, one case observed from beginning to end establishes the fact that this disease is a tubular lesion and can occur without any glomerular inflammatory lesion so far as our methods of examination reveal. In view of the different opinions among writers on this question, this case seems to us to be of considerable importance.

We believe that Epstein's chronic nephrosis and our cases, representing examples of Munk's lipoid nephrosis, are identical.

We feel that pure cases of lipoid nephrosis are not common but that the routine use of the polarization attachment to the microscope in the

examination of urinary sediment from suspected patients will uncover other cases of this type. Secondary lipoid degeneration of the tubules will often be found.

The prognosis in most of the cases is good.

The cause is still veiled in obscurity. The majority of authors view it as a disturbance of the metabolism of the colloids. That names the defect without explaining it.

There is no specific treatment, but the high protein low fat diet of Epstein combined with reduction in the intake of sodium chloride are rational procedures. The administration of large doses of thyroid is still on trial. Epstein recommends it and claims that it is beneficial. Our experience is too limited for us to offer any opinion.

CARCINOMA OF CORTEX OF SUPRARENAL GLAND WITH VIRILISM

REPORT OF A CASE WITH NECROPSY *

HENRY M FEINBLATT, M D

BROOKLYN

Although malignant epithelial growths of the cortex of the suprarenal gland are the most frequent of the neoplasms affecting this organ, the association of clinical virilism with the postmortem demonstration of such a tumor is sufficiently unusual to be deserving of report

REPORT OF CASE

History—A woman physician, aged 32, single, a Russian Jewess, with whom I first became acquainted in April, 1924, at that time she seemed normal, her appearance and personality being distinctly feminine

The family and past personal history were negative

One evening in April, 1925, after dancing, the patient experienced a gnawing sensation in the right lumbar region, covering an area about the size of the palm. The pain did not radiate but seemed to come in waves. Later that night, it became more severe but disappeared by morning.

Subsequently, many similar attacks recurred, usually following strenuous exertion. For a period of six weeks, in May and June, however, she was entirely free from this disturbance.

In July a gradual change began to come over the patient. Her face lost much of its femininity and became angular in outline, the voice grew lower in pitch, and a growth of hair appeared on the chin and cheeks. The menstrual periods, previously regular, became scanty and irregular in April, 1925, and disappeared altogether after July.

In August the change in the patient's appearance was quite noticeable. Her face was thinner and her complexion sallow. There was a definite subicteric pigmentation of the skin and a growth of hair on the face similar to that commonly observed in women after the menopause. There was also a thickening of the axillary and abdominal hair. At that time she began to suffer from headaches, which were so severe as to compel her to lie down.

One day early in September, after a strenuous day's work, the patient collapsed in the subway. She was taken home and remained in bed for a week. That night she had severe pain in the right upper abdominal quadrant. For a week afterward, there was an afternoon rise of temperature to about 102 F. At that time the liver was not enlarged. From that time on she suffered from constipation.

Complete physical rest was advised, during which time the patient was under observation. The skin discoloration deepened, assuming a brownish tint, and the liver's edge became palpable below the costal margin. When she was up for any length of time, edema of the feet and ankles would set in.

The patient was admitted to the Long Island College Hospital, Oct 28, 1925, complaining of pain in the right lumbar region and upper abdominal quadrant, swelling of the ankles and legs, abdominal distention after eating, rebellious constipation and brownish discoloration of the skin.

* From the Long Island College Hospital, Brooklyn, N Y

Physical Examination—The patient was a tall, slender, greatly emaciated woman, exhibiting a discoloration of the skin that looked like a combination of general pigmentation and jaundice. There was a fairly thick growth of hair on the upper lip, the prominence of the chin and the side of the jaw. The abdominal hair was of the masculine type of distribution, that is, it came up along the midline above the umbilicus, extending as far as the ensiform cartilage. The pubic and axillary hair was abnormally coarse and thick.

The eyes were sunken from emaciation. The conjunctivae were jaundiced. The voice had become definitely low pitched.

There was a systolic murmur over the pulmonic area of the precordium, but examination of the heart was otherwise negative. A few inconstant rales were heard at the right apex and infraclavicular region. There was a considerable dulness at both pulmonary bases, with loss of tactile fremitus on the right side.



Fig 1—The patient a few days before death, showing the growth of hair in the region of the beard.

The abdomen was abnormally full. The lower border of the liver was felt at the level of the umbilicus, it was tender in the epigastric region. Below the liver, in the right flank, a mass could be palpated, which felt like an enlarged kidney.

Laboratory Examinations—The urine was dark yellow and strongly positive for bile by the foam and Gmelin's tests, and contained a very faint trace of albumin. A few leucin crystals were found.

The blood count showed 4,480,000 red cells, 82 per cent hemoglobin (Sahl's method, corrected), and 19,600 white cells, the differential count, 80 per cent polymorphonuclear neutrophils, 13 per cent small lymphocytes, 5 per cent transitionals and 2 per cent eosinophils. November 21, five days before death, the red cell count was 4,100,000, 7 per cent of the cells being reticulated. The white blood cell count was 54,000, 97 per cent of the leukocytes being polymorphonuclear neutrophils. The platelet count was 868,000.

The systolic blood pressure was 110, diastolic, 75. Blood chemical examination gave normal values for urea nitrogen, uric acid and sugar.

Roentgenologic examination showed a great increase in the height of the diaphragm on the right side. The liver was shown to be enlarged and there was generalized abdominal density, which was believed to be attributable to ascites.



Fig 2—Section through the tumor and the adherent right kidney, the kidney, at the lower pole of the growth, has been compressed, just below the ureter, a section of the tumor and clot mass obtained from the right ventricle at necropsy has been placed.

Course of Illness—From the date of admission, the patient gradually lost strength and became drowsy. The skin pigmentation, especially on the face, became more intense, the facial hypertrichosis also increased.

The liver grew larger and its surface was more irregular than on earlier examinations. Edema of the feet and ankles developed. The temperature was normal except during the last two weeks of the illness, at which time it was subnormal.

Intermittent pain of increasing severity, finally becoming constant, developed in the right upper abdominal region. The patient became duller and duller and, November 21, passed into coma. Treatment was merely symptomatic and supportive. Death from exhaustion took place November 26.

The clinical diagnosis was carcinoma of the cortex of the suprarenal gland, with metastasis to the liver and possibly elsewhere.

Postmortem Examination—The body was extremely emaciated. The skin had a general icteric tint. There was a hemorrhagic conjunctivitis, more pronounced on the right side. The left pupil was dilated, the right, contracted. The abdomen was greatly distended and the veins were abnormally full, especially on the right side.

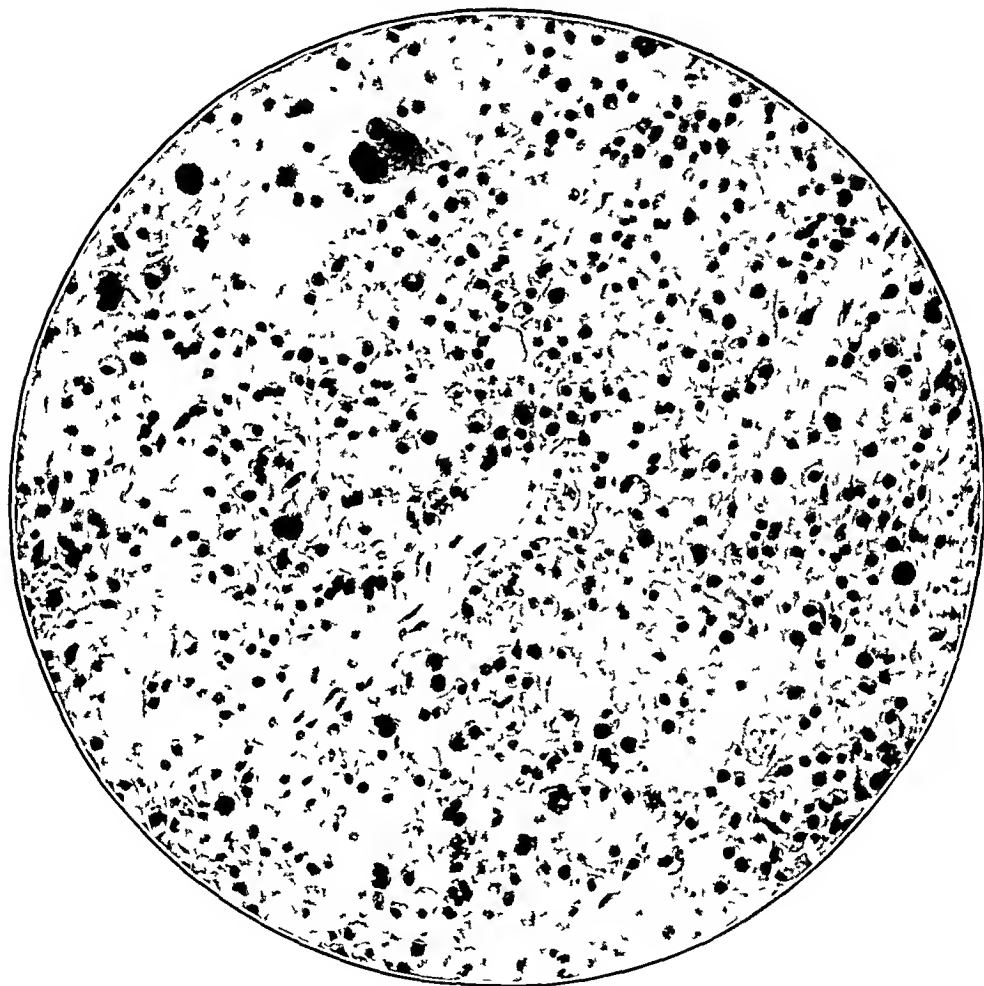


Fig 3—Cellular portion of the growth, great variety in the size of the cells, large number of giant cells, numerous capillaries directly adjacent to the cells, and absence of stroma should be noted.

The heart was somewhat smaller than normal. It weighed 300 Gm. The right auricle and ventricle were dilated. The ventricle contained a roundish mass of fused tumor tissue and blood clot, measuring 2.5 cm in diameter. This tissue is shown in figure 2. The lungs were normal.

The liver weighed 2,500 Gm, it showed a high grade of passive congestion. Microscopically, the cords of liver cells were widely separated by edema and distended capillaries. The nuclei of the cells were abnormally small and took the stain poorly. The spleen weighed 190 Gm and was congested. The stomach contained an excess of mucus. The left kidney was slightly congested but other-

wise normal. No suprarenal gland could be found on this side. The diaphragm was at the level of the third intercostal space on the left side, of the third rib, on the right.

The right kidney was fused with the tumor of the right suprarenal body. The tumor and the kidney together weighed 2,000 Gm. The mass measured $8\frac{1}{2}$ inches (21.5 cm) in length, by $5\frac{1}{2}$ inches (13.9 cm) in breadth, by 5 inches (12.7 cm) in depth. The upper third of the kidney was buried in the neoplastic substance. On section, however, one could see bands of fibrous connective tissue separating the growth from the kidney. Microscopically, both kidneys showed parenchymatous degeneration of the convoluted tubules.

The tumor was located in the region of the right kidney and was adherent partly to the diaphragm and partly to the right kidney. It was separated from the liver by a small band of fibrous tissue. It felt firm and elastic. On section, the surface at the periphery was fairly firm and cellular, the interior was soft and succulent, being the seat of necrosis. The whole tumor was highly vascular. Extending from the renal vein to the heart, the entire vena cava was filled with clotted blood and pieces of tumor mass. One of these fragments had dropped into the right ventricle.

The ovaries were small and congested and showed many surface hemorrhages. The uterus was small and anteflexed, its endometrium was in the intermenstrual stage.

Examination of the brain was negative except for a small cyst of the pituitary gland, which showed hyaline degeneration on microscopic study.

Microscopic Examination of Tumor.—Microscopically, the tumor was very cellular. The cells were of the large granular type, with ample cytoplasm and with dense, hyperchromatic nuclei showing many mitotic figures. A considerable degree of diversity in the size of the individual cells was apparent. There were numerous capillaries, to which the cells were directly adjacent. There was very little stroma. The cells were arranged predominantly in sheets. In some fields the tumor was composed largely of giant cells, in which the chromatin stained deeply and was irregularly distributed. The center of the growth showed massive necrosis. Figure 3 is the microscopic picture of the neoplasm.

The fragment found in the heart was covered with a layer of fibrin and red blood cells. The mass itself was highly cellular and vascular, like the parent growth, giant cells predominated.

No metastases could be found, except for the extensions of the growth to the vena cava and the right ventricle.

The pathologic diagnosis was carcinoma of the cortex of the right suprarenal gland, causing death from exhaustion.

In carcinoma of the cortex of the suprarenal gland, early and extensive spread and metastasis are the rule. My case was unusual in that, in spite of the large size of the tumor, the only extensions were in the vena cava and no distant metastases could be found. Another unusual feature was the absence of one of the suprarenal glands.

SUMMARY

A young woman progressively developed virile characteristics, including facial hypertrichosis, the masculine type of abdominal and axillary hair, a low pitched voice and a masculinoid facies. Later, a tumor was palpated in the region of the right kidney. Necropsy revealed a large carcinoma of the cortex of the right suprarenal gland with extension by way of the vena cava but without distant metastasis.

UREA RETENTION

A SIMPLE METHOD FOR ITS ESTIMATION BY THE MERCURY
COMBINING POWER OF BLOOD

PHILIP S HENCH, M D

AND

MARTHA ALDRICH, B A

ROCHESTER, MINN

Simple clinical methods that furnish accurate data are desirable in the study of renal function, particularly for the physician to whom the complicated methods of analyzing the blood are not available. The method reported in this article is of interest as an accurate index to the urea of the blood. The standard determination of blood urea by the urease method is an admirable test but requires very careful technic, certain laboratory facilities and is somewhat time consuming. The method herein reported requires only elementary laboratory knowledge and very simple equipment, only about fifteen minutes are required, and it gives adequate clinical results. It is the estimation of the mercury combining power of deproteinized blood.

NOTES ON THE LITERATURE

Liebig¹ in 1853 made use of the ability of mercury to combine with nitrogenous products in a method for the determination of urea in urine. In 1921 Friedlander² reported a titrametric method with mercuric chloride for the determination of urea in urine. In 1922 we³ demonstrated the quantitative relationship between the urea in saliva and in blood, a finding since corroborated by Schmitz,⁴ Stitt,⁵ Landsberg⁶ and Viotti.⁷ In 1923 we⁸ developed a mercury titration

* From the Division of Medicine, Mayo Clinic

1 Von Liebig, J. Ueber einige Harnstoffverbindungen und eine neue Methode zur Bestimmung von Kochsalz und Harnstoff im Harn, *Ann d Chem* **85** 289-328, 1853

2 Friedlander, Ernst. Titration des Harnstoffes im Urin für klinische Zwecke, *München med Wchnschr* **68** 1225-1226 (Sept 23) 1921

3 Hensch, P S, and Aldrich, Martha. The Concentration of Urea in Saliva, *J A M A* **79** 1409-1412 (Oct 21) 1922

4 Schmitz, H W. Comparative Concentration of Urea in the Blood and Saliva in a Series of Pathologic Cases, *J Lab & Clin Med* **8** 78-82, 1922-1923

5 Stitt, E R. *Practical Bacteriology, Blood Work and Animal Parasitology*, ed 6, Philadelphia, P. Blakiston's Son & Co, 1920

6 Landsberg, Marcel. Ueber den Harnstoffgehalt im Speichel, *Klin Wchnschr* **2** 306 (Feb 12) 1923

7 Viotti, G. Sulla possibilità di stabilire la concentrazione in urea del sangue colla misura della concentrazione in urea della saliva, *Pathologica* **16** 47-50 1924

8 Hensch, P S. Salivary Urea and the Mercury Combining Power of Saliva. A New and Simple Index of Renal Insufficiency, *M Clin N Amer* **7** 123-134 (July) 1923. Hensch, P S, and Aldrich, Martha. A Salivary Index to Renal Function, *J A M A* **81** 1997-2003 (Dec 15) 1923

method for the determination of urea in saliva. We found that mercury combined with other nitrogenous constituents of saliva besides urea, but that because of the preponderant influence of the urea of the saliva on its mercury combining power this could be used as an index to the salivary urea and therefore to the blood urea. We advocated the use of the mercury combining power of saliva, the "salivary urea index," as an index to urea retention in the body in cases in which blood was not readily available.

The principle, clinical application and accuracy of the salivary urea index as an index to urea retention have been confirmed by several investigators. Calvin and Isaacs⁹ reported about 200 determinations on children at the Michael Reese Dispensary, Chicago. Corkill,¹⁰ Fairley¹¹ and Meyers¹² of Australia and Rockwood and Rockwood,¹³ individually report satisfactory results, while Pacetto¹⁴ of the University of Pavia in Italy and Simmel and Kuntscher¹⁵ of the Medical Polyclinic at Jena also report corroborating results, with certain slight variations in their interpretation of the formula for the salivary urea index. Graham and MacCarty¹⁶ of the University of Alabama confirmed its use with saliva and applied the method successfully to spinal fluid.

There are conditions such as coma or states of dehydration in which blood can be more readily obtained than saliva. Furthermore, the blood presents a more stable medium physiologically, and is less subject to contamination than saliva, so that determinations on blood give more direct evidence of urea retention in the body.

METHOD FOR DETERMINING THE MERCURY COMBINING POWER

The method is based on the principle that mercury combines with such products as urea, creatinine and uric acid, when a solution of a mercuric salt is added to a solution containing these nitrogenous products.

9 Calvin, J. K., and Isaacs, Bertha L. Studies on the Salivary Urea Index in Children, *Am J Dis Child* **29** 70-77 (Jan.) 1925.

10 Corkill, A. B. The Estimation of the Salivary Urea as an Index to Renal Prognosis, *M J Australia* **1** 236-238 (March 7) 1925.

11 Fairley, K. D., and Splatt, Beryl. A Simple Technique for the Estimation of the Blood Urea. The Hench-Aldrich Method, *M J Australia* **1** 517-519, 1924.

12 Meyers, E. S. Personal communication to the author.

13 Rockwood, E. W., and Rockwood, P. R. Laboratory Manual of Physiological Chemistry, ed. 5, Philadelphia, F. A. Davis Company, 1924, pp. 131-132, also personal communication to the authors.

14 Pacetto, G. La concentrazione ureica della saliva quale indice della funzione renale nello studio del ricambio azotato, *Riforma med* **41** 649-652 (July 13) 1925.

15 Simmel, H., and Kuntscher, G. Die Prüfung der Nierenfunktion durch Bestimmung des Harnstoffs im Speichel, *Deutsche med Wchnschr* **51** 1909-1910 (Nov. 13) 1925.

16 Graham, G. S., and MacCarty, Sarah H. On the Application of the Hench-Aldrich Urea Index to the Spinal Cord, *J Lab & Clin Med* **10** 548-551 (April) 1925.

As mercury is added combination continues until the mercury combining power of the solution is satisfied, after which excess mercury appears in the solution. The excess mercury is readily detected by adding a drop of the solution to be tested to a drop of saturated sodium carbonate on a white spot-plate. A dark reddish brown precipitate indicates the presence of excess mercury. The method is here applied to the protein free blood filtrate obtained by the use of trichloroacetic acid. The mercury combining power of this filtrate will vary with changes in the concentration of blood urea.

TECHNIC ¹⁷

The mercury combining power of the blood is determined essentially as in saliva except that the protein in the blood is first precipitated with trichloroacetic acid. The precipitation of the protein by the use of acetic acid and heat, or by the tungstic acid method of Folin and Wu, was not satisfactory.

Our method is as follows. 5 cc of oxalated blood is added drop by drop to 5 cc of 10 per cent trichloroacetic acid in a centrifuge tube. The contents of the tube are thoroughly mixed and centrifugalized for about five minutes. If a centrifuge is not available the mixture may be filtered, although this is less rapid and convenient, and may necessitate the use of more than 5 cc of blood to obtain 5 cc of filtrate. Five cubic centimeters of the clear protein free filtrate is then titrated with 5 per cent solution of mercuric chloride. The mercury solution is added from a buret until a test drop of the mixture when added to a drop of saturated sodium carbonate on a porcelain spot-plate gives a reddish brown precipitate which appears within three seconds. It is important to mix the mercuric chloride and filtrate very thoroughly before the test drop is removed. A yellow precipitate may occur before the reddish brown, but the titration must be continued until the precipitate becomes reddish brown promptly within three seconds. A minimum of 1.5 cc of mercury solution can be added before test drops are removed. As few test drops as possible should be removed.

The mercury combining power of blood is defined as the number of cubic centimeters of 5 per cent solution of mercuric chloride that will combine with 100 cc of deproteinized blood. If a buret is used, the number of cubic centimeters of 5 per cent solution of mercuric chloride used for the 5 cc of blood filtrate is multiplied by 20 to obtain the mercury combining power of 100 cc of blood filtrate. The mercury combining power of 100 cc of filtrate is then multiplied by 2 to estimate the mercury combining power of 100 cc of blood, since the blood was diluted by an equal volume of trichloroacetic acid to obtain the filtrate.

17 Hench, P. S., and Aldrich, Martha. The Mercury Combining Power of Deproteinized Blood, *Proc Soc Exper Biol & Med* **22** 556-558, 1924-1925

Therefore, the mercury combining power of 100 cc of blood equals 40 times the mercury combining power of 5 cc of blood filtrate

The titration of the filtrate may be made from a buret or more conveniently in the index tube of the apparatus¹⁸ described for the determination of the salivary index (fig 1) If the salivary index apparatus is used, the technic is identical to that used for saliva With the black tipped dropper, one drop of saturated sodium carbonate is placed in each depression of the porcelain plate The supernatant blood filtrate is poured from the centrifuge tube¹⁹ into the calibrated index tube up to the line marked "5 cc" Then with the red tipped dropper the 5 per cent solution of mercuric chloride is added until the mark "30" in the index tube is reached With the cork inserted the tube is inverted about three or four times for thorough mixing With the small pipet one

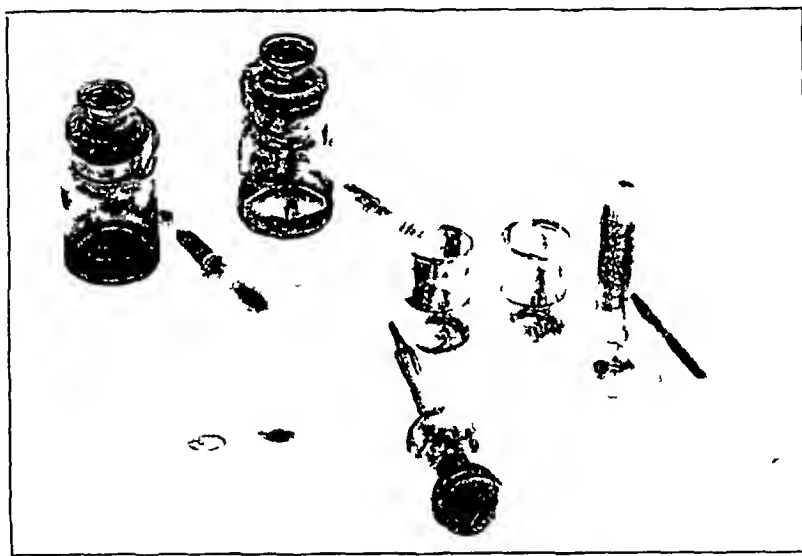


Fig 1—Apparatus used to determine the salivary urea index

drop is added to a drop of saturated sodium carbonate on the porcelain plate The remainder of the contents of the pipet is returned to the index tube If a brownish red precipitate promptly appears on the porcelain plate, the end point has been reached, but if no color or a canary yellow appears, the titration must be carried further In this case from 3 to 6 drops of mercuric chloride solution should be added, the solution mixed and tested again with sodium carbonate, one thus adds mercuric chloride into the index tube until the test drop first shows a definite brownish precipitate, developing promptly within three seconds The amount of fluid used for the test drops removed should be replaced as accurately as possible by water or mercury solution as convenient,

18 Hench, P S, and Aldrich, Martha Apparatus for the Determination of the Salivary Urea Index, *J A M A* 82 1194-1195 (April 12) 1924

19 The precipitate remaining in the centrifuge tube is very adherent but the tubes are readily cleaned by boiling from five to ten minutes

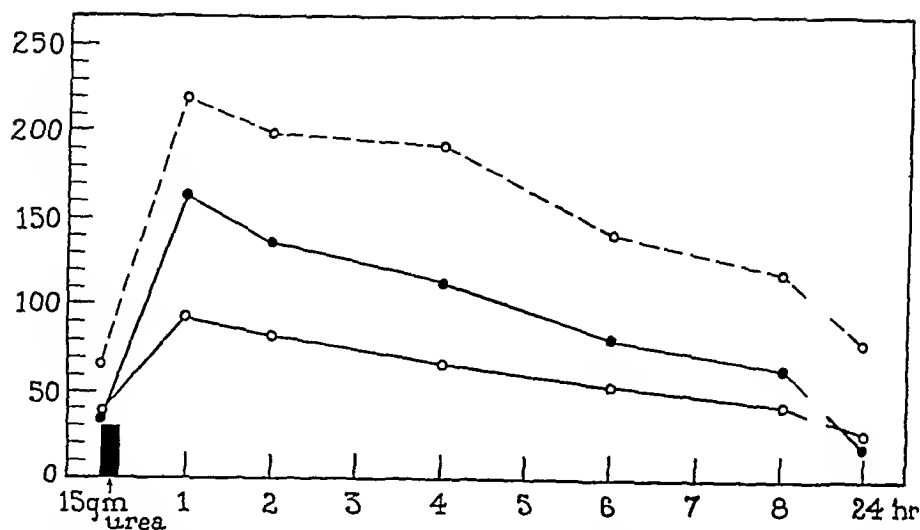


Fig 2—Parallel rise and fall of the urea, nonprotein nitrogen and mercury combining power of the blood in a dog after uremia was induced by feeding urea. Solid dot solid line, blood urea milligrams for each 100 cc of blood, open dot broken line, mercury combining power—cubic centimeters of mercuric chloride for each 100 cc of blood, open dot solid line, nonprotein nitrogen milligrams for each 100 cc of blood.

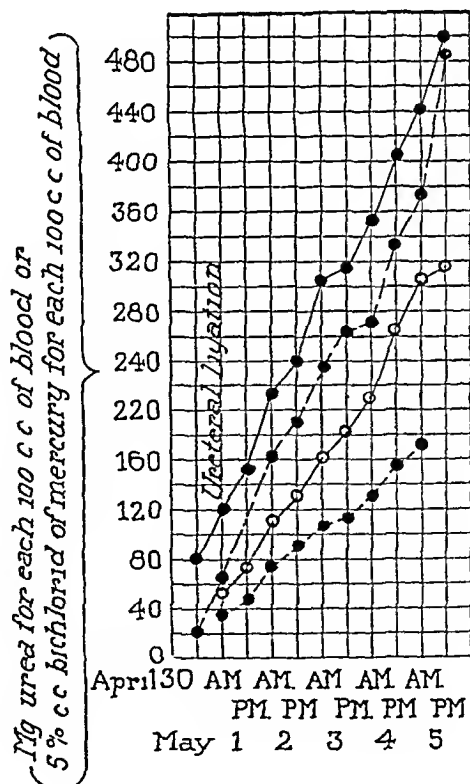


Fig 3—Increase in the mercury combining power, urea, creatinine, and non-protein nitrogen of the blood of a dog after bilateral ureteral ligation. Solid dot solid line, mercury combining power of blood, solid dot broken line, blood urea, open dot solid line, nonprotein nitrogen of blood, and solid dot broken line, blood creatinine.

and when this replacement is made the number of cubic centimeters of mercury solution used for 100 cc of filtrate may be read directly from the index tube. To estimate the mercury combining power of blood this figure must be multiplied by 2, as the mercury combining power of blood equals twice the mercury combining power of filtrate because of the previously mentioned dilution of blood by trichloroacetic acid.

THE CLINICAL SIGNIFICANCE OF THE MERCURY COMBINING POWER OF BLOOD

The mercury combining power of the blood is an accurate index of the retention of nitrogen and especially of urea in the blood. This is illustrated experimentally by the changes observed when chemical uremia is induced in a dog by giving 15 Gm of urea through a stomach tube (fig 2). There was a parallel rise and fall of the values of the blood urea determined by the urease method, the mercury combining power of the blood and the total nonprotein nitrogen. It will also be noted that in spite of the rapid fluctuations in these values, an almost constant difference of 60 points between the values for the blood urea in terms of milligrams for each 100 cc and the values for the mercury combining power of blood was maintained throughout.

Estimations of the blood urea by means of the urease method, the total nonprotein nitrogen and the creatinine, and the mercury combining power of the blood were made in a dog after bilateral ureteral ligation (fig 3). A resultant rise in all values occurred. Again will be noted (except for the last very high value) the almost constant difference between the mercury combining power of the blood and the value for the blood urea, the former being 60 points higher.

In normal persons and patients with retention of urea a proportional correlation between the mercury combining power of the blood filtrate and the blood urea (by the urease method) likewise was found over a large range of blood urea values from 10 to 560 mg for each 100 cc of blood (fig 4).

It will be seen that the mercury combining power of the filtrate rises in direct agreement with the rise of the blood urea with but slight occasional deviation. It will also be seen that as the blood urea theoretically reaches zero, the blood filtrate will theoretically still take up 30 cc of 5 per cent solution of mercuric chloride. Since the mercury combining power of blood equals twice the mercury combining power of filtrate, the mercury combining power of blood without any urea in it would be 60 cc, the constant difference noted in the preceding figures. In patients with nephritis and retention of nitrogen, urea is the chief retained product. Other substances that combine with mercury, such

as amino-acids,²⁰ uric acid and creatinine, either are not increased in nephritis or the increase is relatively unimportant from the standpoint of the mercury combining power. The linear proportionality between the blood urea and the mercury combining power of blood filtrate demonstrated on the charts is striking. Apparently the amount of mercury combined with substances other than urea is a constant (60 cc) and further variations depend almost entirely on the urea content of the blood. It is obvious, therefore, that the mercury combining power of deproteinized blood can be used in such cases as a rapid clinical method for the estimation of the blood urea. The latter may be calculated by means of the formula probable blood urea (in milligrams for each

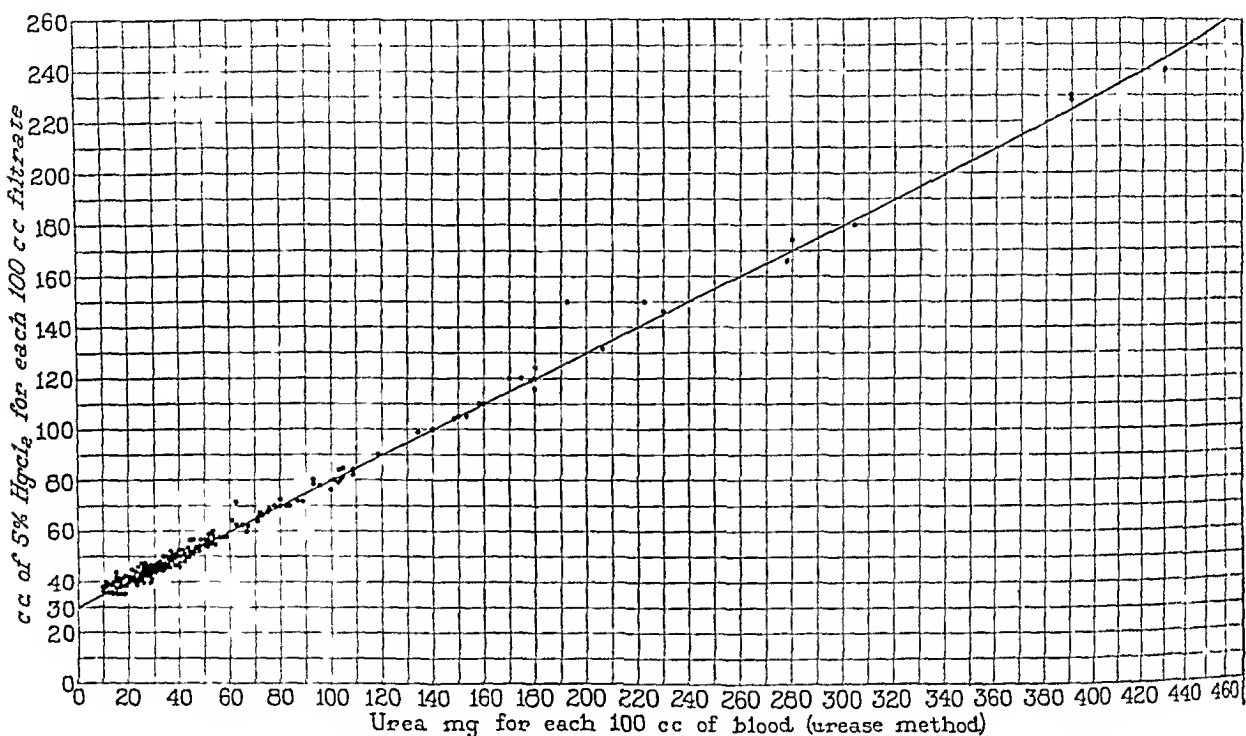


Fig 4—Simultaneous comparisons of the mercury combining power of blood filtrate with blood urea values of normal persons and patients with urea retention. Values erected on the abscissa represent milligrams of urea for each 100 cc blood, on the ordinate, the mercury combining power. If exact proportionality existed, the values would be on the line. A few high values are not represented, including a value of 310 for the mercury combining power of the filtrate of the blood of a patient with a blood urea of 560 mg for each 100 cc.

100 cc) equals mercury combining power of blood minus 60. Since the mercury combining power of blood equals twice the mercury combining power of filtrate, probable blood urea (in milligrams for each 100 cc) equals twice the mercury combining power of filtrate minus 60.

20 Greene, C. H., Sandiford, Kathleen, and Ross, Helen. The Amino-Acid Content of the Blood in Normal and Pathologic Conditions, *J Biol Chem* 58:845-857 (Jan) 1924.

Example—If 5 cc of blood filtrate requires 4 cc of 5 per cent solution of mercuric chloride to titrate to the end point, the mercury combining power of 100 cc of filtrate would therefore be 20 times 4, or 80. The mercury combining power of 100 cc of blood would be 2 times 80, or 160, and the probable blood urea would be 160 minus 60, or 100 mg for each 100 cc

Figure 5 shows in a different way the extent of variation between the actual blood urea determined by the urease method and the blood urea calculated from the mercury combining power by the formula. The estimations made on patients with leukemia or polycythemia are omitted from figures 4 and 5 and will be discussed separately

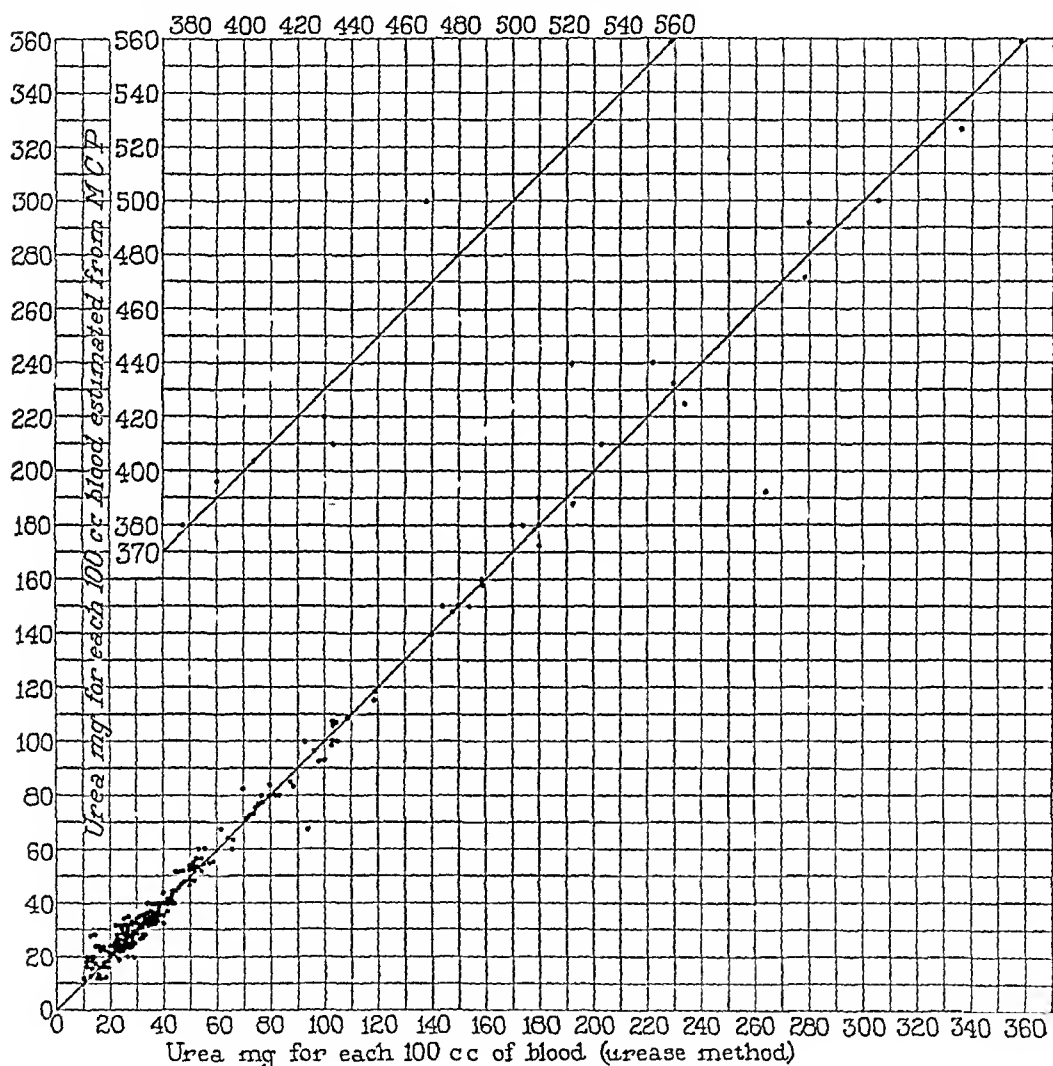


Fig 5—Comparison of values for the blood urea calculated from the mercury combining power with those actually determined by the urease method. If exact proportionality existed the dots would all be on the line. Values for urea by the urease method are plotted on the abscissa, those calculated from the mercury combining power on the ordinate.

Variations—It will be noted that over the wide range of values determined there are a few variations from theoretical values. The number and degree of these deviations are within the limits of acceptable

clinical and laboratory methods. These variations must occur because, while urea is the substance chiefly responsible for the variations in the mercury combining power of the blood above the constant of 60 cc, it is not the only substance that combines with mercury. Variations in the others may slightly affect the value of the constant 60 and therefore the calculation of the blood urea. However, for all practical purposes such variations in the constant may be ignored and the foregoing formula considered correct. This is shown by a comparison of 250 estimations of the calculated urea with the urea values directly determined by the urease method.

In 76 per cent the calculated value was equal to or within 5 mg of the urea determined by the urease method. In 20 per cent the difference was from 6 to 10 mg, and in 4 per cent the difference was more than 10 mg. The 4 per cent may be considered an inaccuracy of the method, but in no instance did it lead to a clinical error. That is, in no instance were the differences sufficient to give an erroneous clinical impression.

The mercury combining power may also be used as a guide to changes in the total nonprotein nitrogen but, in general, we have found a much closer relation between the urea and the mercury combining power of blood than between the total nonprotein nitrogen and the mercury combining power of blood.

THE MERCURY COMBINING POWER OF PLASMA AND SERUM

The urea content of whole blood, plasma and serum is generally considered to be substantially identical, especially in normal persons.²¹ Plass²² and Madsen²³ have recently pointed out that this constancy of distribution of urea is not maintained in certain pathologic states, particularly when there are rapid fluctuations in the nitrogen content of the blood. We have occasionally observed a discrepancy between the urea of whole blood and that of plasma or serum not only in abnormal but normal states (table 1).

The mercury combining powers of serum and plasma are about the same, though lower than the mercury combining power of whole blood. In normal persons the mercury combining power of plasma or serum is apparently between 60 and 90 as compared to the mercury combining power of whole blood, which is normally between 70 and 100. In case of nitrogen retention the mercury combining power of plasma and

21 Marshall, E. K., Jr., and Davis, D. M. Urea. Its Distribution in and Elimination from the Body, *J Biol Chem* **18** 53-80, 1914.

22 Plass, E. D. Variations in the Distribution of the Nonprotein Nitrogenous Constituents of Whole Blood and Plasma During Acute Retention and Elimination, *I Biol Chem* **56** 17-29 (May) 1923.

23 Madsen St Tschudi. Researches on the Distribution of RN (Nonprotein Nitrogen) and Urea in the Body, *Acta med Scandinau* **6-7** 318-326, 1923-1924.

serum is increased proportionately to the urea content, and the urea content may be approximated from the mercury combining power by the subtraction of a constant 50 instead of the figure 60 given in the formula for the estimation of the blood urea from the mercury combining power of whole blood, for example, probable plasma (or serum) urea (in milligrams for each 100 cc) equals mercury combining power of plasma (or serum) minus 50²⁴

The constant may perhaps be used as an index to the amount of the substances present in the trichloroacetic acid filtrate which combine with mercuric chloride but which do not change appreciably in any condition

TABLE 1—*The Mercury Combining Power of Whole Blood, Plasma, Serum and Corpuscles in Normal and Nephritic States*

Whole Blood				Plasma				Serum				Corpuscles		
Mg for Each 100 Cc				Mg for Each 100 Cc				Mg for Each 100 Cc				Mg for Each 100 Cc		
Urea				Urea				Urea						
Mercury Combining Power	Calculation from Mercury Combining Power	Actual Determination	Nonprotein Nitrogen	Mercury Combining Power	Calculation from Mercury Combining Power	Actual Determination	Nonprotein Nitrogen	Mercury Combining Power	Calculation from Mercury Combining Power	Actual Determination	Nonprotein Nitrogen	Mercury Combining Power	Urea, Actual Determination	Nonprotein Nitrogen
92	32	35	41.6	88	38	33	25.8					108	24	41.6
92	32	37	43	84	34	38	28.5					152	32	48
104	104	100	76	156	106	111	73					228	103	64
92	32	28		80	30	32								
88	28	29		80	30	34								
88	28	28		72	22	24								
144	84	89		144	94	88								
84	24	23		68	18	19								
100	40	41						102	52	51				
86	26	22						76	26	27				
104	44	44						100	50	49				
148	88	91						152	102	105				
344	284	272		360	320	297								
92	32	33	38.3	92	42	36	27.9	94	44	34.5	31.5	120	32	42.8

observed (except those to be noted further on) The lower constant observed in the estimation of plasma (or serum) urea from the mercury combining power of the plasma (or serum) likewise suggests that these unknown substances occur in greater quantity in the corpuscles Changes in the unknown substances are apparently of minor importance, except those to be noted presently, and for routine clinical use we have found the analysis of whole blood more convenient than that of plasma or serum

24 The formula was based on sixty-seven cases, a few illustrative comparisons are given

THE MERCURY COMBINING POWER IN LEUKEMIA AND POLYCYTHEMIA

The urea nitrogen of the blood is normally about 50 per cent of the total nonprotein nitrogen, although this ratio may vary considerably. In certain states, leukemia,²⁵ polycythemia²⁶ and acute yellow atrophy of the liver,²⁷ and certain types of the eclampsia of pregnancy,²⁸ it has been observed that there may be a profound alteration of this ratio, and the blood urea nitrogen may fall to much smaller proportions than 50 per cent of the total nonprotein nitrogen. In four cases of lymphatic and two cases of myelogenous leukemia and in five cases of polycythemia which we have studied, a normal or slightly increased concentration of urea was often encountered in the presence of a distinctly increased total nonprotein nitrogen. This increase of the total nonprotein nitrogen may be explained in part on the basis of an increase in amino-acids which we know are increased in leukemia and polycythemia, but this increase does not serve to account for the total increase in the rest nitrogen. Analyses of the whole blood, serum, plasma and corpuscles were made in the cases of leukemia and polycythemia (table 2). It was noted that the formula for the estimation of the blood urea from the mercury combining power of the blood could not be correctly used (columns 6 and 7, table 2). When the urea was calculated (column 6, table 2) from the mercury combining power of blood in these cases, it gave much higher values than when it was determined by the urease method (column 7, table 2). Calculations of the probable plasma or serum urea from the mercury combining power of plasma or serum gave values comparable to those actually determined. In two cases the estimation of the blood urea from the salivary index gave figures comparable to those found in the actual determination of blood urea.

25 Green, C. H., and Connor, H. M. Diseases of the Liver. V. A Comparative Study of Tests for Hepatic Function in Certain Diseases of Hematopoietic System, *Arch Int Med*, to be published. Greene, Sandiford and Ross (footnote 20). Sandiford, Kathleen, Boothby, W. M., and Giffin, H. Z. The Amino-Acid Nitrogen in the Blood and Its Possible Relation to the Elevation of the Metabolism in Myelogenous Leukemia, *J Biol Chem* **55** 23-24, 1923.

26 Greene and Connor (footnote 25, first reference).

27 Feigl, J., and Luce, H. Neue Untersuchungen über akute gelbe Leberatrophie, I. Ueber den Reststickstoff des Blutes und seine Komponenten. Weitere Beiträge zur vergleichenden Pathologie des Amino-saurespiegels im Blute, *Biochem Ztschr* **79** 162-201, 1917. Stadie, W. C., and Van Slyke, D. D. The Effect of Acute Yellow Atrophy on Metabolism and on the Composition of the Liver, *Arch Int Med* **25** 693-704 (June) 1920.

28 Caldwell, W. E., and Lyle, W. G. The Blood Chemistry in Normal and Abnormal Pregnancy, *Am J Obst & Gynec* **2** 17-34 (July) 1921. Killian, J. A., and Sherwin, C. P. Some Chemical Studies in Normal and Abnormal Pregnancies. I. Significant Chemical Changes in the Blood in the Toxemias of Pregnancy, *Am J Obst & Gynec* **2** 6-16 (July) 1921.

It is therefore apparent that, in the presence of abnormal numbers of corpuscles, either red or white, as in polycythemia and leukemia, the trichloroacetic acid filtrate contains substances that combine with larger amounts of mercury than normal. When these disturbing elements are eliminated by using plasma, serum or saliva, the mercury combining power may be used to estimate the urea. Analysis of the cells themselves suggests that the mercury combining power of leukocytes is greater than that of erythrocytes. The total nonprotein nitrogen is also higher than the blood urea values would lead one to expect. This is due partly to an increase in amino-acids, but this increase alone is not sufficient explanation.

Many nitrogenous substances in the blood (amino-acids, polypeptids, proteoses, thiasine,²⁹ creatine, and so forth) normally occur wholly or in greatest concentration within the cells and are recognized as responsible for the increased rest-nitrogen of the cells compared to that of the plasma. The increase in the mercury combining power of the blood in leukemia and polycythemia is apparently due to the larger proportion of cells, white or red, in such blood. Tables 1 and 2 show that in polycythemia there was but little difference between the mercury combining power of the erythrocytes and that of normal erythrocytes.

THE MERCURY COMBINING POWER OF STANDARD SOLUTIONS OF NORMAL NITROGENOUS CONSTITUENTS OF BLOOD

Determinations of the mercury combining power of some standard solutions of the known constituents of the blood show that these substances combine in very different proportions with mercury. Urea, creatinine, ammonium salts and the amino-acid, glycine, were tested. This method of approach, however, cannot be used to determine what elements actually make up the total nonprotein nitrogen of the blood, because of the impossibility of synthesizing so complex a mixture as blood and testing the mercury combining power of the different elements composing it.

THE USE OF THE METHOD INTERPRETATION AND COMMENT

Determination of the clinical significance of albuminuria is one of the commonest problems of the practitioner. Five per cent of apparently healthy persons and more than 50 per cent of Mayo Clinic patients have albuminuria. However, in less than half of these cases is the albuminuria of consequence. The presence or absence of renal lesions can be

²⁹ It is of interest to note here that a new sulphur containing compound, thiasine, recently isolated from the blood and contained wholly in corpuscles, is isolated partly by its ability to combine with mercuric chloride. Benedict, S. R., Newton, Eleanor B., and Behre, Jeanette A. A New Sulphur Containing Compound (Thiasine) in the Blood, *J. Biol. Chem.* 67: 267-277 (Jan.) 1926.

accurately determined only by the use of tests of renal function. Disregarding classifications, one of two phenomena is present in nephritis, first, the retention of products of protein metabolism with consequent increase in the nonprotein nitrogen (urea, and so forth) in the blood and, second, the retention of salts and water, in diffuse renal lesions both phenomena may be observed.

The routine management of patients with nephritis by means of a milk diet of from 2 to 4 quarts daily is not scientific treatment. If urea retention is present, such a diet includes too much protein, if edema is present it contains too much fluid. Water retention speedily manifests itself by edema. A marked degree of nitrogen retention, however, may occur without producing clinical symptoms of uremia. The determination of the presence or absence of retention is the *sine qua non* of rational treatment.

The determination of the blood urea by the urease method is not used extensively in small hospitals or by physicians in general practice because the technic seems complicated and time consuming. When the relatively inaccurate determination of the hemoglobin in the blood by the blotting paper method is compared with the more accurate chemical methods, Cabot's defense is recalled that the blotting paper method is the most inaccurate but, withal, the most useful. Thus it is that simple laboratory methods alone become popular and widely used. They are desirable so long as the necessary accuracy is not sacrificed to convenience. The simple method presented for determining urea retention by means of the mercury combining power of blood is accurate. In the hands of the inexperienced worker, it is more accurate than the blood urea method because it offers less chances of error in technic. The speed and simplicity of the method especially recommend it for clinical use. It should therefore be of particular value to the general practitioner in routine work, to the small hospital, and for use as a rapid method in emergencies by the consultant in the large hospital. It is not meant to replace urea determinations when these may be readily done, although it is felt to be equally accurate for practical purposes. It is comparable in practicability to the universally used phenolsulphonphthalein test of Rowntree and Geraghty, and the water test and concentration test of Volhard and Fahr. By means of these four tests,³⁰ which may be readily carried out by any practitioner with a minimum of laboratory equipment and training, all essential information regarding renal function can be obtained.

30 Hench, P. S. A Note on Renal Functional Tests for the General Practitioner, *Northwest Med* **23** 539-542 (Dec.) 1924, Practical Considerations of Renal Physiology and Function Their Application to the Management of Nephritis, *J. A. M. A.* **87** 7-14 (July 3) 1926.

CONCLUSIONS

1 The presence or absence of urea retention in body fluids can be determined by the estimation of the mercury combining power

2. The mercury combining power of blood is defined as the number of cubic centimeters of 5 per cent solution of mercuric chloride capable of combining with 100 cc of deproteinized blood. The normal values vary between 70 and 100

3 The blood urea can generally be estimated from the mercury combining power by use of a simple formula

4 The mercury combining power of serum and plasma are approximately equal, though lower than the mercury combining power of whole blood. The urea of serum and plasma can also be approximated by formula

5 The mercury combining power of the blood in polycythemia and leukemia varies with the total nonprotein nitrogen rather than with the blood urea, on account of the abnormal composition of the blood in such cases. The mercury combining power of the serum or plasma or of the saliva (the salivary urea index) is not so affected, and may be used for the estimation of the urea

6 The deviations of the method are within the limits of acceptable clinical and laboratory procedures and the speed and simplicity of the test recommend the estimation of the mercury combining power of blood for general use

THE FORMATION OF ORGANIC ACIDS AND THE RETENTION OF CHLORIDES IN LOBAR PNEUMONIA ¹

CAI HOLTEN, M D

COPENHAGEN, DENMARK

It is a well known fact that small amounts of chlorides are found in the urine during the course of lobar pneumonia. It was shown in 1850 by Redtenbacher. It is a constant and as a rule so well pronounced a phenomenon that it can be used as a symptom of some diagnostic importance.

Of course a good deal of interest is attached to the pathologic basis of this phenomenon, and a good many investigators have been occupied with it, e. g., von Terray,¹ Jochmann and Bittorf,² von Hoesslin,³ Scheel⁴ and others, but as far as I know no completely satisfactory explanation has been given.

The first question that arises is whether it is a genuine retention of chloride that exists during pneumonia. In such a highly febrile disease the patient of course eats little, and one might think that the slight excretion of chlorides was due to the slight food intake. It seems to me that previous authors have not given this possibility sufficient consideration.

I therefore put my patients with pneumonia on a constant daily ingestion of chloride. By this the existence or nonexistence of a retention can be verified and the elimination of chlorides can be followed from day to day. The patients were given the following diet: 500 cc of milk, 500 cc of oatmeal gruel, 200 cc of cream, 2 eggs, salt-free bread and salt-free butter, tea and water, plus 5 Gm of sodium chloride, that is to say, from 6 to 7 Gm of sodium chloride per day.

The patients were given this diet from the time of admission till three days after the crisis, or after the temperature had become almost normal.

Each portion of urine was brought as soon as possible after having been passed to a glass, which was kept in a refrigerator, and a little toluene was added. In this manner twenty-four hour samples from all the patients to be examined were collected. The content of chlorides was determined daily by the method of Bang and Laison. It was soon

¹ From the third (medical) department of the City Hospital of Copenhagen.

Read before the Congress for Physiology and Experimental Medicine, Sweden, April, 1925.

1 Von Terray. *Ztschr f klin Med* **26** 346, 1894.

2 Jochmann and Bittorf. *Deutsches Arch f klin Med* **89** 489, 1906.

3 Von Hoesslin. *Deutsches Arch f klin Med* **93** 404, 1908.

4 Scheel, V. *Hospitalstidene*, 1904, p 1016.

seen that a real retention of chlorides takes place As an example I give chart 1 from patient 1, a man, aged 57, who became ill six days before admission, it shows considerable retention and after the fall of the temperature, which here was not absolutely critical, an elimination that far exceeds the intake This is a constant feature, I shall later return to it (charts 3, 4 and 5)

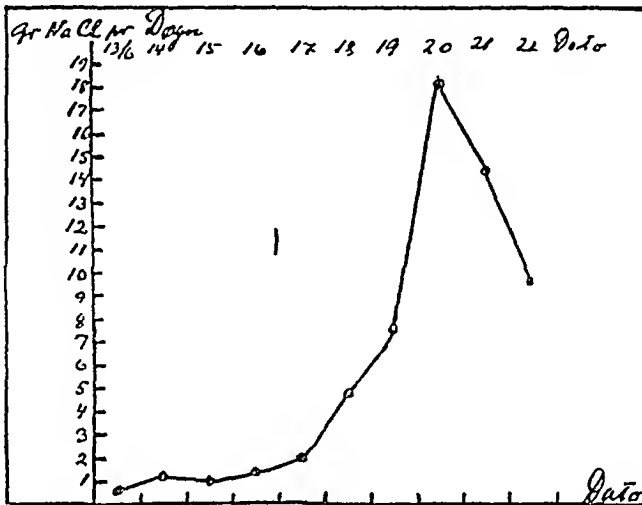


Chart 1 (case 1)—Grams of sodium chloride excreted in urine during twenty-four hours from June 13 to 26, 1, crisis, June 16-17

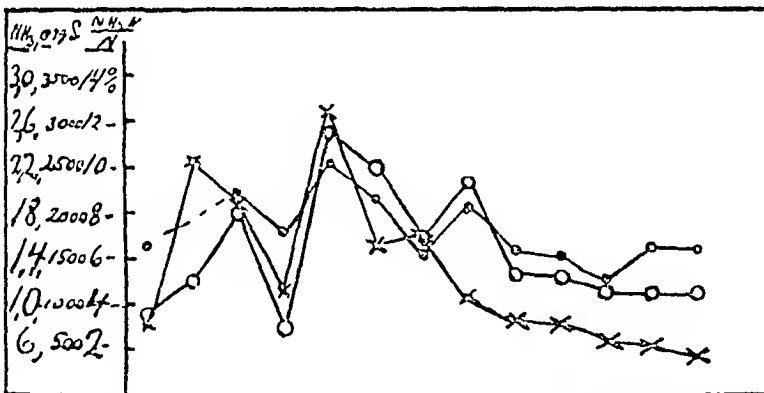


Chart 2—Open dot and line, grams of ammonia, X and line, cubic centimeters of tenth normal organic acid, and solid dot and line, the relation $\frac{\text{ammonia nitrogen} \times 100}{\text{nitrogen}}$ in a case of lobar pneumonia

I also undertook the determination of the conductivity of the urine after the method of Christiansen⁵ By this the peculiar fact came out that the normal relation between the amount of chlorides determined by titration and the conductivity is altered during the fever period in such a manner that the amount of chlorides is relatively much more reduced than the conductivity As an example the following figures from case 1 are given

5 Christiansen, Johanne Wien klin Wchnschr 35 461 (May 18) 1922

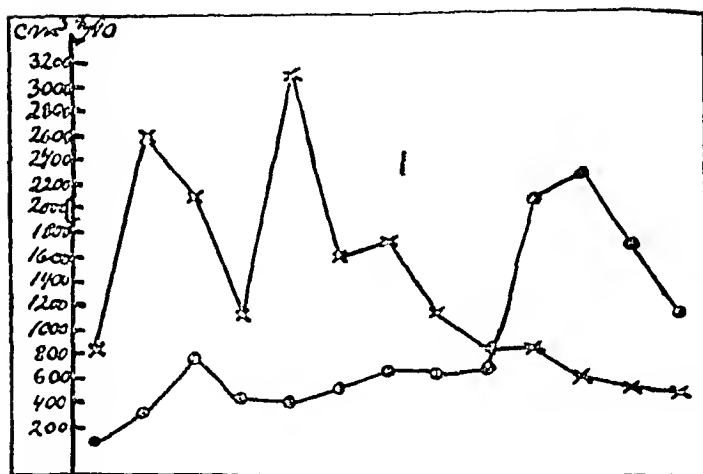


Chart 3—Solid dot and line, cubic centimeters of tenth normal sodium chloride, X and line, cubic centimeters of tenth normal organic acid in case of lobar pneumonia, 1, crisis

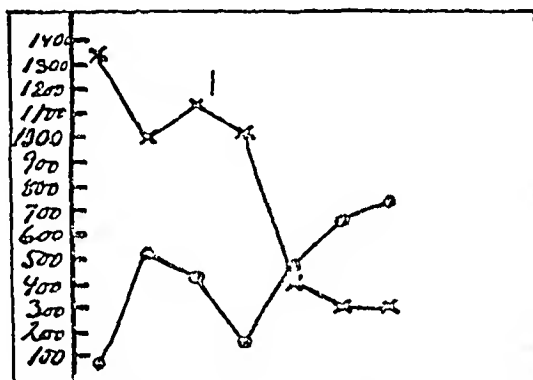


Chart 4—Solid dot and line, cubic centimeters of tenth normal sodium chloride, X and line, cubic centimeters of tenth normal organic acid in case of lobar pneumonia, 1, crisis



Chart 5—Solid dot and line, cubic centimeters of tenth normal sodium chloride, X and line, cubic centimeters of tenth normal organic acid in case of lobar pneumonia 1, crisis The patient was a child and was given 3 Gm of sodium chloride daily

	June 13	June 14	June 15	June 16
Conductivity (expressed as grams of sodium chloride)	5.3	8.6	8.5	8.0
Sodium chloride (titrimetrically), grams	0.7	1.1	1.0	1.5

And for comparison the following figures from two afebrile patients with neurasthenia are given

	A	B
Conductivity	14.8	16.2
Titrated sodium chloride	10.0	10.5

At the crisis the normal relation is reestablished in the patients with pneumonia, in case 1, in which the crisis occurred June 16, the figures were

	June 17	June 18	June 19	June 20	June 21
Conductivity	8.1	10.7	15.3	23.4	21.2
Titrated sodium chloride	2.0	4.8	7.5	18.0	14.2

Hence it seems that an alteration of the salt excretion takes place during the febrile period of pneumonia so that the normal dominating influence of the chlorides on the conductivity of the urine is abolished. In order to find out the cause of this I followed the excretion of other salts than the chlorides. First, I undertook in three patients the determination of p_H of the urine to know if an elimination of bicarbonate took place. This might be provoked by a hyperventilation leading to an alkalosis. The result is given in table 1.

TABLE 1—*Hydrogen Ion Concentration of the Urine in Three Cases of Pneumonia*

Case	June 13	June 14	June 15	June 16	June 17	June 18	June 19	June 20	
1	5.6	5.6	5.5	6.5	6.5	6.5	6.5	6.5	Crisis June 16
	May 17	May 18	May 19	May 20	May 21	May 22	May 23	May 24	May 25
2	5.1	5.3	5.5	5.5	5.7	5.7	5.6	5.6	5.5 Died
	May 7	May 8	May 9						
3	5.5	5.5	5.5						

Table 1 shows that the hydrogen ion concentration is so high that bicarbonate cannot exist in these urines. Furthermore, it is seen that the acidity of the urine in case 1 decreases after the crisis.

After this the excretion of bicarbonates in cases of pneumonia was impossible.

In thirteen patients daily determinations were undertaken of (1) chlorides, (2) phosphates (acetate of uranium), (3) sulphates (benzidine) and, furthermore, as these two salts did not appear in altered amounts, (4) organic acids, after the van Slyke and Palmer⁶ method, and in order to control and supplement the last determination (5) the amount of ammonia (Björn Andersen and Lauritzen) and (6) nitrogen

⁶ Van Slyke, D. D., and Palmer, W. W. J. Biol. Chem. **41** 567 (April) 1920.

(Krogh method) These determinations were made daily in each case from admission till at least three days after the crisis, the patients still being on the diet described

Regarding phosphates and sulphates no alteration was found, and the excretion of these salts was not considerably altered after the crisis Two examples are given in table 2

TABLE 2—*Phosphates and Sulphates in Urine (Twenty-Four Hours) in Two Cases of Pneumonia*

Case 4		Case 5	
Phosphorus Pentoxide	Sulphuric Acid	Phosphorus Pentoxide	Sulphuric Acid
26 Gm	26 Gm	23 Gm	34 Gm
14 Gm	19 Gm	27 Gm	30 Gm
Crisis } 15 Gm	23 Gm	Crisis } 21 Gm	27 Gm
19 Gm	27 Gm	20 Gm	26 Gm
18 Gm	16 Gm	24 Gm	20 Gm
14 Gm	19 Gm	25 Gm	16 Gm
12 Gm	15 Gm	29 Gm	22 Gm
20 Gm	25 Gm		

However, the van Slyke and Palmer method showed values that by far surpassed normal values. The principle of this method is the fact that quite an insignificant amount of a strong acid is necessary to alter the hydrogen ion concentration from 10^{-8} to 2×10^{-3} in a solution in which only salts of strong acids are found, whereas almost a whole molecule of a strong acid is needed for each molecule of a salt of a weak acid in solutions in which such are found. The urine phosphates and carbonates are practically the only inorganic salts that act as salts of weak acids, these are precipitated by calcium hydroxide, then 0.5 cc of 1 per cent solution of phenolphthalein is added to 25 cc of urine treated in this manner and fifth normal hydrochloric acid is added till the red color just disappears. Then 5 cc of 0.02 per cent solution of tropeolin OO is added and the urine is titrated with fifth normal hydrochloric acid until the same color is reached as in the standard solution with $C_h 2 \times 10^{-3}$. From the amount of hydrochloric acid used the amount of organic acid is calculated, it is generally expressed as cubic centimeters of tenth normal acid. Creatinine behaves in the same manner as organic acids. Van Slyke and Palmer state that normal persons excrete 8.2 cc of tenth normal organic acid per kilogram in twenty-four hours, which is about 500 cc in adults, this does not include creatinine, which according to van Slyke and Palmer amounts to 2 cc of tenth normal acid per kilogram in twenty-four hours. Hence, when creatinine is not corrected for, 600-700 cc of tenth normal organic acid is found per twenty-four hours in normal adults. The method has been thoroughly tested by van Slyke and Palmer and found sufficiently correct for clinical use. I have made a few control experiments with it by determining the amount of organic acid found

in a number of samples of urine and adding a known amount of lactic acid I have found this again with an error of from 2 to 3 per cent

It might be thought that the increase of the amount of organic acid was due to an increased elimination of creatinine. *A priori* it is very improbable, for the formula of creatinine is $C_4H_7N_3O$, its molecular weight is 113, in cases of pneumonia the amount of organic acid found is not seldom about 2,000 cc of tenth normal acid per liter of urine, in one case in which this was the case the diuresis was 1,100 cc per twenty-four hours, so that 24.6 Gm of creatinine should have been excreted to account for this amount of organic acid. The excretion of creatinine in a case of pneumonia was found by Leathes⁷ to be 2.34 per cent of the total nitrogen excretion. The nitrogen excretion in the case just quoted was 15.5 Gm, of this about 9.3 Gm, or 60 per cent, should originate from creatinine if 24.6 Gm of creatinine had been excreted. This is, of course, not the case. The largest excretion of nitrogen I have found in any of my cases was 23 Gm, out of this 0.56 Gm may have been due to creatinine, if we assume that the relation of creatinine-nitrogen to total nitrogen was the same as in the case examined by Leathes. This corresponds to about 50 cc of tenth normal organic acid. In the case concerned 1,100 cc of tenth normal organic acid was found, hence the creatinine can account for only a very small amount of the organic acid found by titration. And here the determination of ammonia and nitrogen shows with certainty that an increased excretion of organic acid takes place. Normally the ammonia-nitrogen is 4-5 per cent of the total nitrogen. In my cases of pneumonia the amount of ammonia-nitrogen in relation to the amount of nitrogen has been increased so that 8-12 per cent has been found, the amount of ammonia has been up to 2.5 Gm. As an example of how the relation $\frac{\text{ammonia nitrogen}}{\text{nitrogen}}$ varies with the amount of organic acid and the absolute amount of ammonia, chart 2 is given. The curves follow each other as closely as can be expected.

Another question is if the intake of camphor, which is rather considerable in some of the cases—in some cases as much as 15 cc of oil of camphor (containing 20 per cent camphor) was given subcutaneously in the course of twenty-four hours—might be the cause of the whole or a considerable part of the excretion of acids. Camphor is to a large degree excreted as camphoglucuronic acid (1 molecule of camphor unites with 1 molecule of glucuronic acid). When 15 cc of oil of camphor per twenty-four hours is given the computation of how much camphoglucuronic acid this can give in the urine will be as follows. 15 cc of oil of camphor = 13.5 Gm of oil of camphor = 2.75 Gm of camphor. The formula of camphor is $C_{10}H_{16}O + H_2O$, the molecular weight is

⁷ Leathes J. Physiol 35 205, 1907

152, the formula of the camphogluconic acid is $C_{16}H_{24}O_8 + H_2O$, the molecular weight is 374, i. e., that about 42 per cent of the camphogluconic acid is due to camphor. Hence, the maximum amount of camphogluconic acid, which 275 Gm can lead to is 6.5 Gm, this corresponds to a 0.0174 normal solution. As the strength of the organic acid in the urine is found to be from eight to ten times this value, the rôle of camphor is unimportant. In accordance with this the amount of organic acid determined in the urine can be seen in no way to depend on the amount of camphor given.

Thus, there is no doubt that an abnormal production of organic acid takes place during the pneumonia. The amounts found vary somewhat from values near the normal, from about 700 cc to 3,000 cc of tenth normal acid per twenty-four hours for adults.

The question is now how the two urinary constituents (*viz.*, the chlorides and the organic acids) which are found to be abnormal in pneumonia vary during the course of it and how they behave at the crisis and immediately after it. Regarding the chlorides it has already been mentioned that a real retention takes place. At the crisis—sometimes a little before, sometimes a little afterward—the chlorides rise far above the amounts given. Charts 1, 3, 4 and 5 show this with great distinctness. The reverse is the case with the elimination of organic acids. This is, as charts 3, 4 and 5 show, high during the febrile period but somewhat varying, at the crisis an abrupt fall to the normal occurs.

What is the cause of the retention of chlorides? Scheel supposes that a water retention on account of stasis is the cause. But this does not bear looking into. The clinical impression the patients suffering from pneumonia give is that they are dry. This might be false or have another significance, but my investigations show that the crisis is not followed by an increase of the diuresis and this was decidedly to be expected if the retention of chlorides, which is compensated at the crisis, was due to retention of water. In six of my cases, selected by chance, the average diuresis per twenty-four hours was 1,380 cc during three days in the febrile period, during three days after the crisis the corresponding figure was 1,125 cc. It is not necessary to explain further that the corresponding figures for the elimination of chlorides show much larger values after the crisis than before.

If one looks at charts 3, 4 and 5, in which the elimination of chlorides and organic acid from three patients with lobar pneumonia is plotted, however, it will be seen that the rise of the chlorides is followed by a contemporary fall of the organic acid, both these things occur at the crisis. This is a phenomenon I have observed in all my cases (besides the thirteen patients mentioned, I have examined five for elimination of chlorides and organic acid only), hence, it is probably correct to put the two phenomena into causal connection with each other. The expla-

nation I want to offer is that chlorides are retained because organic acids are produced. That chlorides actually are retained when an organic acid is formed or, what I think must be the same, is brought into the organism, can be seen from charts 6, 7, 8 and 9. These are obtained from four patients with slight chronic arthritis. Charts 6 and 7 are from two patients who had a diet containing 10 Gm of sodium chloride for from ten to eleven days, after from one to two days the amount of chlorides in twenty-four hours' urine was determined for a couple of days, then

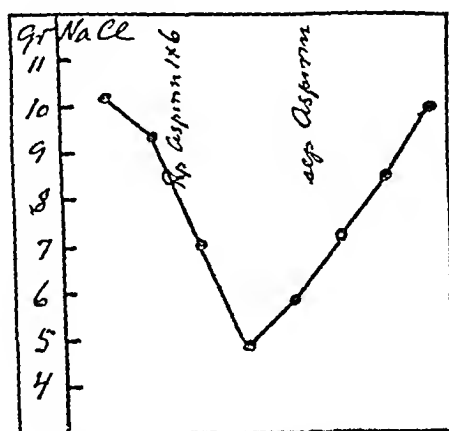


Chart 6—Grams of sodium chloride excreted in twenty-four hours' urine before, during and after the dosage of acetosalicylic acid

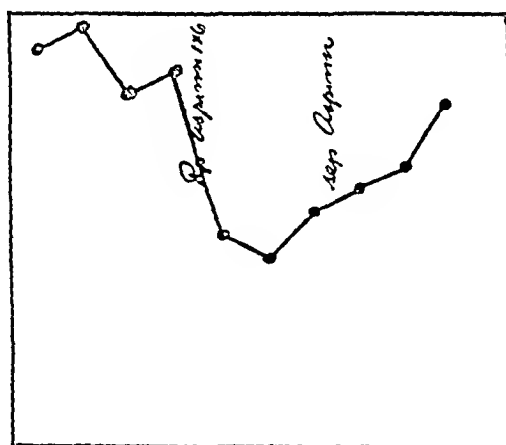


Chart 7—Grams of sodium chloride excreted in twenty-four hours' urine before, during and after the dosage of acetosalicylic acid

6 Gm of acetosalicylic acid was given daily for three or four days. This acid in the organism is split into acetic acid, which is combusted, and salicylic acid, which is eliminated as salicylic and salicyluric acid. After the lapse of three or four days I stopped giving acetosalicylic acid, but the patients had the same diet for three further days in which estimation of chlorides in twenty-four hour samples was continued.

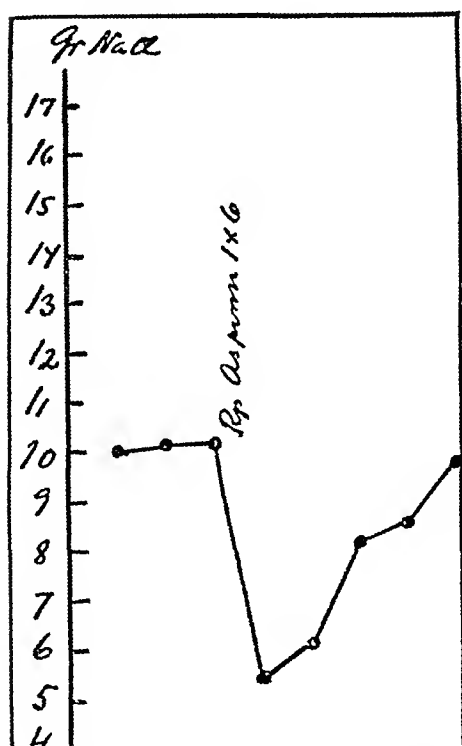


Chart 8—Excretion of sodium chloride in twenty-four hours' urine before and during the dosage of acetosalicylic acid

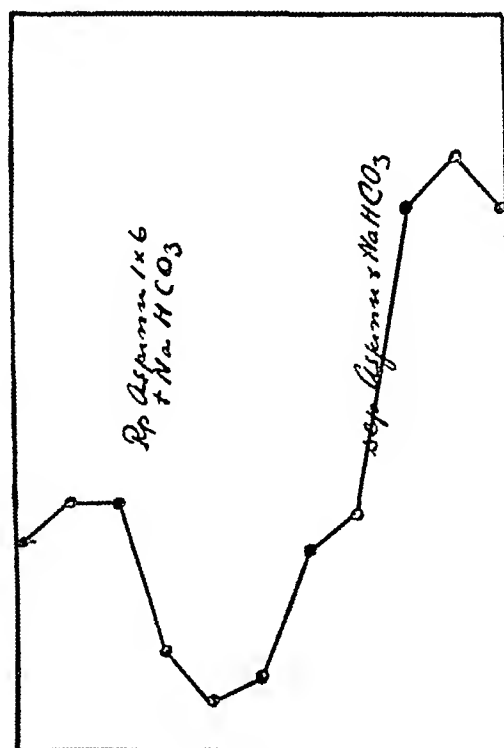


Chart 9—Excretion of sodium chloride in twenty-four hours' urine before, during and after the dosage of acetosalicylic acid together with sodium bicarbonate

Chart 8 is from a patient to whom I gave the same diet and in whom I carried out the experiment in essentially the same manner but continued giving acetosalicylic acid for five days. From these three curves it is seen that the intake of organic acid is immediately followed by a rapid fall of the chloride elimination—a retention is produced, from chart 8 is seen that the retention grows less when the intake of the acid is continued for a long time. The chloride elimination does not rise immediately after the outset of the acetosalicylic dosage to values corresponding to the intake plus the amount retained—this is probably explained by the fact that the acid is slowly eliminated, still on the second day after the dosage of the acetosalicylic acid had ceased the ferrichloride test was positive in these urines.

I am of the opinion that these experiments strongly support my theory, which as already stated is that the retention of chloride in lobar pneumonia is due to the formation of organic acids which in some way or other influence the tissues so that chloride is retained. It is difficult to believe that the retention is due to an action on the kidney.

Some authors have maintained this, for instance von Hoesslin⁸ and von Furth.⁹ These investigators say that the cause of the chloride retention is a deficient power of the kidney to excrete chloride. This cannot be the case, however, as all who have investigated it have found the chloride content of the blood abnormally low, among them Peabody,⁹ Mac Lean,¹⁰ Snapper,¹¹ Christoffersen,¹² Fridericia,¹³ Jacobsen,¹⁴ and Gram and Norgaard.¹⁵ Mac Lean, who has published the largest series of investigations, finds low values (less than 5.62 Gm per liter of plasma) during the febrile period and rising values at the crisis. These investigations have been made with plasma as well as with the total blood.

It might be thought that the organic acids took hold of a large part of the metal ions for elimination so that chloride was retained. But I do not think that this is the case. In two cases of pneumonia I gave the patients 1 teaspoon of sodium bicarbonate three times a day, this did not influence the elimination of chlorides. In an experiment with ingestion of acetosalicylic acid plus sodium bicarbonate, otherwise undertaken in the same manner as the previously described two experiments (charts 6 and 7), I have found that the acetosalicylic acid here also

8 Von Furth. Probleme d. physiol. u. path. Chemie, Leipzig, **2** 609, 1913.

9 Peabody. J. Exper. Med. **17** 71, 1913.

10 Mac Lean, F. C. J. Exper. Med. **22** 366, 1915.

11 Snapper, T. Deutsches Arch. f. klin. Med. **111** 429, 1913.

12 Christoffersen, N. R. Ugeskr. f. Læger. **83** 234 (Feb. 17) 1921.

13 Fridericia, L. S. Ugeskr. f. Læger, 1921. Fridericia, L. S., and Olsen, O. Hospitalstidende, 1912, p. 857.

14 Jacobsen, A. B. Ugeskr. f. Læger, 1921, p. 234.

15 Gram, H. C., and Norgaard, A. J. Biol. Chem. **56** 429 (June) 1923.

caused a decrease of the elimination of chlorides in somewhat the same way as in the other experiments (chart 9) but, as may be seen, the retention was abolished much earlier in this experiment. The urine only showed the ferrichloride test in the specimens from the first twenty-four hours after the outset of the dosage of acetosalicylic acid while the part of the urine passed during the night did not show this test. In this experiment the urine was strongly basic, so that sufficient alkali must have been at the disposal of the kidney. Things here are possibly the same as in diabetic acidosis in which alkali treatment accelerates the elimination of the acids and neutralizes them in the blood, but probably does not act in the tissues. Examples of coma continuing in spite of the alkaline reserve in the blood being brought to normal values by alkali treatment are well known.

Where are the chlorides retained?

Several authors have sought for them but have not been able to find anything conclusive as to any tissue containing them. Scheel among others has examined the lungs but found that the percentage of chloride contained in the pneumonic tissue is less than in the normal lung tissue and even when we regard the large weight of the condensed tissue this can, according to Scheel, account for only a few grams.

However, the amount of sodium chloride retained during the whole course of a lobar pneumonia is not very great. In one case in which the patient was admitted on the day after the onset of symptoms I calculated the retention as 30 Gm in the course of eight days, as the weight of the patient was 65 Kg the increase of the content of chlorides of the tissues will be 0.055 per cent if we assume that all tissues except the bones participate in the retention.

The investigations of later years, particularly by Wahlgren¹⁶ and Padtberg,¹⁷ have shown that the chloride content of the tissues, and especially of the skin, is very variable. It is therefore easily understood that moderate increase of the chloride content easily avoids demonstration, particularly when it is considered that the retention is less when the disease has been of shorter duration.

Furthermore, it is another question as to which acid it is that is produced in lobar pneumonia. I have tried to obtain some knowledge about this but have not yet finished these investigations. I have systematically examined the urine of thirteen patients daily for aceto-acetic acid and acetone with negative results. I have in some cases sought for β -oxybutyric acid after the method of Ohlsson, with negative results. I have examined the filtrate from the precipitation with calcium hydroxide for ethereal sulphates, with negative results.

16 Wahlgren Arch f Pharmakol 63:60, 1910

17 Padtberg Arch f Pharmakol 61 62, 1909

Also, I have extracted the urine with ether and estimated the amount of organic acids before and after this procedure and found that part of the organic acids pass into the ether, I have treated the ether extract with a 30 per cent solution of sodium carbonate, distilled after sulphuric or phosphoric acid was added in sufficient amount, and tried to find formic acid and acetic acid but have found nothing definite. Last, I have tried to find lactic acid after the method of Boas-Vournasso by the formation of iodoform and got a positive result. I have endeavored to estimate the amount of lactic acid but these investigations have not yet been concluded. I can only state that lactic acid is found in the urine in lobar pneumonia but not whether it constitutes the largest part of the organic acid found.

At last we might ask if this formation of organic acid is due to anoxemia.

As Lundsgaard¹⁸ has pointed out we must, as a rule, expect to find cyanosis in anoxemic patients and some only of my patients have been cyanotic. Furthermore, one knows from the investigations of Haldane and Yandell Henderson that anoxemia caused by low oxygen pressures is followed by an alkalosis with lowered excretion of acids in the urine. I have examined the urines from two patients with chronic cyanosis (one patient with congenital heart disease and one patient with tumor mediastini) and one patient with acute cyanosis (capillary bronchitis complicating heart disease) without finding the amount of organic acids in the urines increased.

It is probable, however, that the formation of these acids is due to metabolic alterations during fever. Fridericia and Otto Olsen in cases of fever have found the tension of the carbon dioxide in the alveolar air decreased. Lundsgaard in eight cases of pneumonia has found the carbon dioxide tension in the arterial blood decreased. Both these things are probably due to a formation of acids.

Fridericia and Olsen suppose that an acidosis is found often during fever. This phenomenon as judged from the excretion of organic acids does not exist so constantly and so pronouncedly in other febrile conditions as in pneumonia. I have examined the urines from four patients with fever due to casein injections and from one patient with pulmonary tuberculosis and not found any increase of the organic acid. In one case of septic endocarditis with temperatures between 38.5 and 39.5 C I found the following values: August 1, 492 cc of tenth normal acid, August 2, 578 cc, and August 3, 700 cc. The last value is no doubt increased as the weight of the patient was only 45 Kg. It is in

18 Lundsgaard, C. *Ugesk. f. Læger* 86 527 (July 10), 561 (July 24) 1924

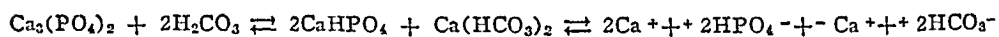
perfect accordance with this and with the theory of the cause of the retention of the chlorides that decreased elimination of chlorides has been found, to a less extent and less constantly in other febrile diseases, e g , typhoid fever and several others. Scheel mentions rheumatic fever but my investigations make it probable that the treatment with salicyl at least to a certain extent plays a rôle here.

CHANGES IN THE CHEMICAL AND PHYSICAL CHARACTERISTICS OF THE BLOOD FOLLOWING THE ADMINISTRATION OF PARATHYROID HORMONE

WITH SPECIAL REFERENCE TO THE CLOTTING OF THE BLOOD *

A CANTAROW, M D
W R CAVEN, M B (Tor)
AND
BURGESS GORDON, M D
PHILADELPHIA

A substance present in the parathyroid gland has been proved to increase effectively the amount of calcium in the circulating blood. The substance was first satisfactorily extracted by Collip¹ and his results have since been confirmed by Hjort,² Berman³ and others. This has led to a more definite understanding of certain features in calcium metabolism about which previously there was considerable doubt. There is much speculation as to the condition in which calcium exists in the blood and the factors that operate to maintain or to modify its normal concentration. According to Howland,⁴ calcium, phosphoric acid and carbon dioxide are present in the blood in a finely balanced equilibrium, illustrated by the following equation



As Wells⁵ states, the calcium salts are held partly in solution, partly in protein suspension, and partly in the form of calcium ion protein compounds. This condition is extremely unstable, subject to alteration by

* From the medical service of Dr Thomas McCrae, the Department for Diseases of the Chest of Jefferson Hospital and the Department of Physiological Chemistry of Jefferson Medical College

¹ A part of the expense for this investigation was defrayed by a grant from a fund in memory of Roland L Taylor, Jr, Gwynedd Valley, Pa

1 Collip, J B. The Extraction of a Parathyroid Hormone Which Will Prevent or Control Parathyroid Tetany and Which Regulates the Level of Blood Calcium, *J Biol Chem* **63** 395 (March) 1925

2 Hjort, A M, Robinson, S C, and Tendick, R F H. An Extract Obtained from the External Bovine Parathyroid Glands Capable of Inducing Hypercalcemia in Normal and Thyreoparathyropriva Dogs, *J Biol Chem* **65** 117 (Aug) 1925

3 Berman, L. Separation of Internal Secretions of Parathyroid Glands, *J Lab & Clin Med* **11** 412 (Feb) 1926

4 Howland J. Etiology and Pathogenesis of Rickets, Harvey Lectures **18** 189 1922-1923

5 Wells, H G. Chemical Pathology, Philadelphia, W B Saunders Company, 1925, p 492

very slight changes in the calcium level, the hydrogen ion concentration, the carbon dioxide and phosphate content, and the amount and nature of the proteins. The blood is normally supersaturated with calcium, the maintenance of the normal level being rendered possible only by the presence of an excess of carbon dioxide. Freudenberg and Gyorgy, as quoted by MacCallum,⁶ have devised a convenient formula to explain the relationship between the calcium, bicarbonate and phosphate ions and the hydrogen ion concentration

$$\frac{\text{Ca}^{++} (\text{HCO}_3)^- (\text{HPO}_4)^{--}}{c\text{H}^+} = K$$

According to this conception the concentration of calcium ions decreases as the bicarbonate and phosphate ions increase and in addition increases as the hydrogen ion concentration increases and vice versa.

These facts are in accord with observations made in many experimental and pathologic conditions but do not hold true in all instances. A chemical expression of this nature is unsatisfactory because it leaves entirely out of consideration the very important and perhaps dominating influence of the blood proteins. However, in addition to these known factors, it was generally believed that there existed some unknown agent of fundamental importance in calcium metabolism, probably related in some way to the secretion of the parathyroid glands. Following the extraction of an active principle of these glands it has been demonstrated that the administration of this hormone is followed by an increase in the concentration of calcium and phosphates in the blood without any of the compensatory changes mentioned above, which are ordinarily believed necessary for the maintenance of the solution and suspension complex.

As stated by Greenwald and Gross,⁷ the only reasonable explanation for this increased saturation of an already supersaturated solution is that the parathyroid hormone in some way retards the precipitation of calcium from the blood. One might assume that it does this either by actually increasing the solubility constant K of the formula shown above or by increasing the ratio of protein-bound calcium to free calcium. The same authors have shown that the calcium level is raised and the excretion of calcium increased without the administration of calcium in the food. This must occur, as they say, at the expense of tissues that represent the fixed calcium deposits of the body. In view of these facts, they conclude that the functions of the parathyroid hormone seem to

6 MacCallum, W. G. On the Pathogenesis of Tetany, *Medicine* **3** 137 (May) 1924.

7 Greenwald, I., and Gross, J. The Effect of the Administration of a Potent Parathyroid Extract upon the Excretion of Nitrogen, Phosphorus, Calcium and Magnesium with Some Remarks on the Solubility of Calcium Phosphate in Serum and on the Pathogenesis of Tetany, *J. Biol. Chem.* **66** 217 (Nov.) 1925.

be, first, the retardation of the precipitation of calcium from the blood and, second, the abstraction by actual solution of calcium from bones and probably other calcific deposits

There has been considerable animal experimentation concerning the action of the hormone. The results have been constant in dogs and cats, but in rabbits, rats and guinea-pigs it has been found difficult to influence the level of the calcium in the blood. An excellent review of the recent literature is given in a comprehensive paper by Collip⁸. In spite of the large amount of work done on the subject there has been little systematic study reported on the effects of the hormone on human beings. In a preliminary study at the Jefferson Hospital⁹ certain clinical observations were made which led to the further investigation of the causes underlying some of the phenomena noted. Of special interest was the tendency for the cessation of hemoptysis in pulmonary tuberculosis which occurred within fifteen minutes after the injection of parathyroid hormone.

In the present study two groups were observed, hospital and out-patients. The patients had chronic pulmonary tuberculosis, active and arrested, bronchial asthma, pulmonary suppuration or pulmonary neoplasm. All patients were under routine hospital management. In the first part of the study various blood determinations were made before and after the injection of the parathyroid hormone¹⁰. These consisted of red and white blood counts, estimation of hemoglobin by the Dare method, blood viscosity by the Hess viscosimeter, clotting time by the Bogg's coagulometer, estimation of calcium¹¹ and inorganic phosphates of the serum, carbon dioxide combining power of the plasma, plasma chlorides, and percentage plasma volume.

On account of the clinical observations previously noted⁹ our interest was particularly centered in the changes that occur from eight to twelve hours following the administration of the hormone. The patients in the first group received 15 units subcutaneously at 4 p. m. followed by 10 units at midnight. The subsequent blood determinations were made at 10 a. m. the following day.

In table 1 the following results will be noted.

Red and White Blood Counts and Hemoglobin—In most cases the determinations made after the injection of the extract showed an increase both in the red and white counts and in the hemoglobin.

8 Collip, J. B. The Parathyroid Glands, *Medicine* 5 1, 1926.

9 Gordon, B., Lewis, A. K., and Roark, J. L. The Effect of Parathyroid Hormone on Certain Signs and Symptoms in Pulmonary Tuberculosis, *J. A. M. A.* 86 1683 (May 29) 1926.

10 The preparation used was parathormone supplied by Eli Lilly & Co., through Drs. G. H. A. Clowes and J. H. Warvel.

11 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Calcium, with a Suggested Modification, *J. Biol. Chem.* 63 461 (March) 1925.

TABLE 1—*Determinations of Some Chemical and Physical Characteristics of the Blood Before and After Administration of Parathyroid Hormone*

Case	Red Blood Cells		White Blood Cells		Hemoglobin		Viscosity		Coagulation Time†		Serum Ca++, Mg per 100 Cc		Serum PO ₄ , Mg per 100 Cc		Carbon Dioxide Combining Power, per Cent by Volume		Plasma Chlorides, Mg per 100 Cc		Plasma Volume, per Cent	
	Before	After	Before	After	Before	After	Before	After	Before	(1)	Before	After	Before	After	Before	After	Before	After	Before	After
										(2)										
1	5,032,000	5,610,000	6,600	8,100	94	90	5.5	4.75	3'	2'10"	10.83	11.21	5.8	9.1	58.6	56.7	618	627	50.8	53.4
2	4,916,000	5,280,000	9,800	10,000	90	93	5	4.5	4'	2'30"	10.39	10.66	6.3	8.9	57.6	52.8	580	600	53.2	50
3	5,061,000	5,010,000	7,600	9,200	95	90	4.8	4.8	3'	2'30"	9.8	12.3	4.2	4.1	55.7	50.4	660	591	53.8	47.3
4	4,080,000	4,130,000	7,600	9,000	70	76	5.5	4.75	3'	2'45"	10.2	9.07	4.8	5	50.8	51.9	586	510	51.9	62.06
5*	4,750,000	5,700,000	8,000	11,400	93	90	4.8	4.8	4'	2'30"	8.9	9.4	4.6	4.6	57.8	59.6	615	571	50.2	61.1
6	3,490,000	4,220,000	10,600	10,600	72	77	5.4	4.8	2'	1'50"	12.3	10.1	4.5	4.3	51.9	51.8	610	631	52.6	54.2
7	5,214,000	5,636,000	8,200	6,100	76	77	5.7	5.7	1'30"	1'30"			4.1	4	60.4	55.8	580	601	49.5	57.7
8	1,900,000	5,476,000	9,500	6,600	87	93			2'	40"					56.2	60.8	610	590	53.9	59.2
9	4,832,000	5,581,000	15,600	18,750	90	91														
10	1,763,000	4,080,000	8,600	9,800	83	83														

All patients in this group had chronic pulmonary tuberculosis except patient 3 (pulmonary suppuration) and patients 9 and 10 (bronchial asthma).
 * No determinations on the plasma could be made following the injection of the extract because in spite of repeated centrifugalization of the blood no plasma could be separated.
 † (1) Five hours after the first injection of parathyroid hormone (15 units), (2) ten hours after the second injection of parathyroid hormone (10 units)

Blood Viscosity—In four of the seven cases in which this determination was made a definite increase in viscosity, especially marked in one case, was noted

Clotting Time—The reduction in clotting time was a striking feature of this study. In some instances it was reduced to less than one minute and in these cases there was great difficulty in obtaining a red count as the column of blood clotted in the pipet before the diluting fluid could be drawn up

Serum Calcium—That a definite rise in serum calcium occurs following the administration of parathyroid hormone has been well established by several investigators. In making this determination our aim was to show a possible correlation between the concentration of calcium at a given time and the other changes that occurred in the blood rather than to demonstrate the elevation of calcium. In this, no striking change in the serum calcium was noted except in two instances. One patient (patient 6) showed a rise of 2.8 mg, and the other (patient 10) a decrease of 2.2 mg. It is not unlikely that the rise in calcium that undoubtedly occurred in every case was missed in several instances because the determination was made at an interval too long after the injection of the hormone. This was subsequently shown by a detailed study of the calcium concentration

Inorganic Phosphates—Only a small number of determinations were made and the results were inconstant

Carbon Dioxide Combining Power of Plasma—In six cases there was a slight decrease in the carbon dioxide combining power and in two patients an increase was noted

Plasma Chlorides—No constant change was noted in the concentration of plasma chlorides, some cases showing an elevation and others a drop

Percentage Plasma Volume—The results obtained in this study were variable. However, since blood volume determinations were not made, no definite conclusion can be arrived at regarding the significance of these figures

In this group of studies three points are outstanding

First, a definite decrease in coagulation time was observed in every case, which in some instances was very marked

Second, there seemed to be a general tendency toward increased concentration of the blood as suggested by the rise in red and white counts, hemoglobin and blood viscosity. Although this is not borne out by our estimations of percentage plasma volume, the latter is not of great value because of probable variation in blood volume

Third, it is apparent that the concentration of calcium in the serum has no constant relation to the rate of coagulability. At the point of determination the clotting time was found to be generally decreased and the serum calcium, though in most cases increased above the control level, was not always altered in proportion to the drop in clotting time. From this it is obvious that the clotting time is not influenced directly by the level of serum calcium. The reason for this is suggested when the mechanism of coagulation is considered. Since calcium participates actively in this phenomenon, it seems reasonable to assume that when a marked variation in clotting time and in the calcium content of the blood occurs there should be a variation in the amount of calcium incorporated in the clot. When the serum calcium is determined that portion included in the clot is naturally excluded. An investigation of the changes that occur in the calcium content of whole blood following the administration of the parathyroid hormone seemed worthy of consideration.

In the second group of cases determinations were made of whole blood calcium, serum calcium and coagulation time at three hour intervals following injection of the parathyroid hormone. The dosage in all cases was 15 units given subcutaneously. In most cases four consecutive determinations were made apart from a preliminary control. In two instances additional estimations were made at the end of twenty-four hours. The results are illustrated in table 2.

TABLE 2—*Coincident Determinations of the Clotting Time and of the Whole Blood and Serum Calcium at Three Hour Intervals Following the Administration of Parathyroid Hormone*

Case	Control	3 Hours	6 Hours	9 Hours	12 Hours	24 Hours
1 Clotting time	5'14"	2'30"	2'45"	2'42"	1'15"	3'
*Blood calcium	7.64	7.7	9.8	10.05	12.24	10.61
*Serum calcium	10.4	15.7	11.4	11.4	10.9	10.52
2 Clotting time	3'45"	1'10"	1'30"	1'30"	3'	
Blood calcium	6.43	11.36	10	10.23	8.62	
Serum calcium	10.45	10.22	9.04	10.4	10.24	
3 Clotting time	4'	2'10"	2'	1'30"	1'	
Blood calcium	6.6	6.2	8.1	8.1	11.1	
Serum calcium	10.2	11.3	11.3	10.8	9.6	
4 Clotting time	2'40"	2'20"	2'	1'30"	2'10"	
Blood calcium	6.52	5.7	9.52	11.2	10.34	
Serum calcium	10.43	14.54	11.4	11.04	10.76	
5 Clotting time	3'30"	4'	1'40"	3'	3'	2'45"
Blood calcium	9.54	11.99	12.2	9.8	8.07	7.22
Serum calcium	10.45	10	9.5	10.78	9.13	8.55
6 Clotting time	2'	2'30"	1'30"	1'30"	2'	
Blood calcium	9.61	10.09	10.52	11.17	8.18	
Serum calcium	10.09	10.09	8.8	9.52	9.04	

All patients had chronic pulmonary tuberculosis except patient 1 (normal).

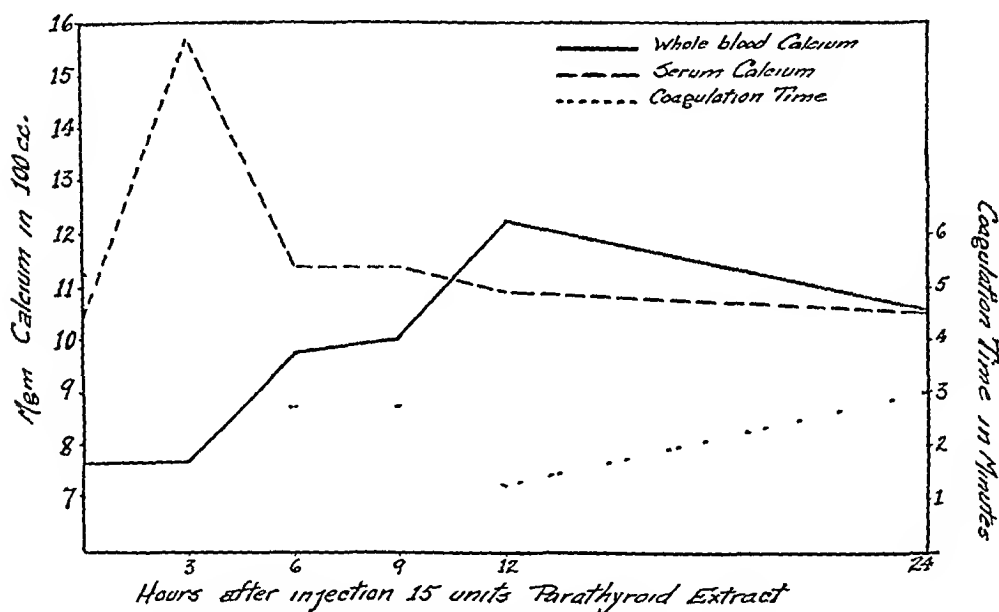
* Blood and serum calcium values are expressed in milligrams per hundred cubic centimeters.

Serum Calcium—The general tendency noted was a sharp rise in serum calcium within the first six hours. This elevation, however, did not occur in every case but since blood was taken only at three hour

intervals, intermediate variations may have been missed. In all cases the calcium had returned close to the original level within twelve hours.

Whole Blood Calcium—The normal limits of whole blood calcium were found by us¹² to be from 6.5 to 9.5 mg per hundred cubic centimeters, the concentration in each case being definitely below that in the serum. In every instance after the hormone injections an increase occurred, gradually in most cases but abruptly in some. In every case the whole blood calcium level rose at some time above that of the serum calcium.

Coagulation Time—The point at which the coagulation time was lowest bore no constant relation to the serum calcium level at that particular time. However, in each instance the point of most rapid coagulation occurred at the time when the concentration of calcium in the whole blood was greatest (accompanying chart).



Characteristic changes in the whole blood and serum calcium and coagulation time following the administration of parathyroid extract in case 1, table 2.

As a result of these observations it seems that the period of most rapid coagulation occurs between ten and fifteen hours after the injection of parathyroid hormone. At this time the whole blood calcium is elevated to its highest point. It appears, therefore, that the clotting time bears a more definite relationship to the calcium level of the whole blood than to that of the serum since it was noted that the greatest elevation of the serum calcium occurred between two and five hours after the injection of the extract. There is a tendency to attach greater significance to

12 Caven, W. R., and Cantarow, A. A Simple Method for the Determination of Calcium in the Whole Blood, *J. Lab. & Clin. Med.*, to be published.

the calcium content of the serum than to that of the whole blood. As the present study suggests, this is apt to be misleading in determining the dosage and time of administration of the hormone.

CONCLUSION

1 So far as can be determined under the conditions of this study there seems to be no significant change in carbon dioxide combining power or in the plasma chlorides following the administration of parathyroid hormone.

2 There is a tendency toward increased concentration of the blood as evidenced by an increase in red and white counts, hemoglobin, and in the blood viscosity.

3 A definite decrease in clotting time was noted in most cases.

4 The time of most rapid coagulation corresponded in every case to the point at which the whole blood calcium was highest, rather than to the highest point of the serum calcium.

THE QUANTITIES OF SERUM ALBUMIN, GLOBULIN AND FIBRINOGEN IN THE BLOOD PLASMA IN ACUTE AND CHRONIC NEPHROPATHIES *

GEORGE FAHR, M D

AND

W W SWANSON, M D

MINNEAPOLIS

The proteins of the blood plasma are hydrophilic colloids. They tend to hold the water of the plasma within the blood capillaries by virtue of their osmotic pressure and inability to diffuse through animal membranes, despite the hydrostatic pressure tending to filter the water out of the capillaries.

We understand the osmotic pressure of hydrophilic colloids as being the sum of the pressure exerted by the particles as molecular kinetic units moving freely in the solution volume and the pressure due to the hydration of the hydrophilic colloids. If we knew the number of hydrophilic colloid particles in a solution of given volume we should not know their osmotic pressure because in addition to the properties of molecular kinetic units the particles have an attraction for water and each particle is surrounded by a shell of water. This shell of water reduces the true volume of solvent materially and in so doing increases the osmotic pressure in proportion to the decrease in volume. In addition the Donnan equilibrium counterpressure is a factor that must be considered in evaluating the water holding power of the plasma colloids.

Ultrafiltration of plasma fluid minus the proteins can take place in the glomerular and tissue capillaries when the hydrostatic pressure within the capillaries rises above the osmotic pressure of the colloids of the plasma. Everything else remaining constant, the rate of filtration of plasma fluid into the tissue spaces and glomerular capsule will be proportional to the difference between the hydrostatic pressure and the osmotic pressure of the colloids. We decided to study the changes in the quantities of serum albumin, globulin and fibrinogen in the plasma of patients with nephritis and nephrosis before undertaking an investigation of the osmotic pressure of the plasma colloids in nephropathies with edema formation. The osmotic pressure of the proteins of the plasma would be proportional to their concentration provided there were no changes in degree of dispersion of the colloids or changes in the degree of hydration.

* From the Department of Medicine of the University of Minnesota Medical School and the Minneapolis General and University Hospitals

* Carried out with the aid of a grant from the Ella Sachs Plotz Foundation

Changes in the amount of albumin would be more significant than equal changes in the amount of globulin because the albumin molecule is only from one-half to one-third as large as the globulin molecule¹ For this reason a knowledge of the albumin-globulin ratio may be of value in calculating osmotic pressure of the proteins of the plasma when the total protein content of the plasma is known

An article on the concentration of the plasma proteins in nephritis by Linder, Lundsgaard and Van Slyke² appeared shortly after we had begun our analyses When it came to our attention our work was well under way We have carried out analyses on twenty-six patients and submit this article as a confirmation of their work

In classifying our nephropathies we have followed the Volhard and Fahr³ system What we have termed subacute glomerulonephritis would correspond to chronic glomerulonephritis stage 1 in their classification What we have termed chronic glomerulonephritis they would classify as stage 2 or stage 3 chronic glomerulonephritis Only cases 13, 17 and 19, table 3, belonged in stage 3 of their classification The other cases belong in their stage 2 group We have used the word hyperpiesia to denote what Volhard and Fahr term benign hypertension Sir Clifford Albutt deserves the greatest credit for differentiating a group of cases with high blood pressure which usually terminated in heart failure rather than uremia from cases of true nephritis Out of piety to him we have used the word "hyperpiesia" which he used to designate such cases All our patients with hyperpiesia came into the hospital in an advanced stage of heart failure and died there Edema formation is only of considerable degree when heart failure develops For this reason we only investigated the plasma protein content in cases of hyperpiesia with heart failure

Our diagnoses were confirmed by postmortem microscopic examination of the kidneys in the seven cases it was possible to obtain a post-mortem Our experience in checking predicted anatomic change with actual anatomic change as found on microscopic examination post mortem has been fairly extensive and the results have been such that we believe that we can predict with considerable accuracy the essential anatomic changes and their degree in the glomeruli, in the tubuli, and in the small blood vessels of the kidneys of patients with glomerulonephritis, with genuine nephrosis, and with arteriolar sclerosis of the kidneys We therefore feel that the diagnoses of the cases in this series are deserving of considerable confidence

1 Cohn, E J The Physical Chemistry of the Proteins, *Physiol Rev* **5** 349 (July) 1925

2 Linder, G C, Lundsgaard, C, and Van Slyke, D D The Concentration of the Plasma Proteins in Nephritis, *J Exper Med* **39** 887 (June) 1924

3 Volhard and Fahr Die Brightsche Nierenkrankheit, Berlin, 1914

ANALYTIC METHODS

All analyses were done on oxalated fluids and these were never permitted to stand in the icebox longer than twelve hours before the analysis was started. In most instances duplicates were made and an average taken as the true value. Stasis of the blood in the vein from which blood was drawn was avoided as far as possible.

The determination of plasma proteins and proteins in body transudates was carried out by the method of Wu.⁴ The amounts of serum albumin, globulin and fibrin are expressed in grams per one hundred cubic centimeters of blood.

TABLE 1—*Plasma Proteins in Normal Patients*

Patient	Albumin	Globulin	Albumin	Fibrin	Total
			Globulin		
F K	50	22	23	02	72
A M	52	22	24	02	74
M M	55	23	24	02	78
E W H	48	23	21	03	71
M V	45	22	20	02	67
J H	46	24	19	03	70
M L	48	24	20	04	72
M	48	22	22	03	70
W W S	50	22	23	02	72
Mean	49+	23+	22	03+	72+

Arithmetic mean and coefficient of deviation calculated from twenty three normal cases of Linder, Lundsgaard and Van Slyke, Epstein, Tahr and Swanson

Albumin	Globulin	Total
45±05	26±04	71±05

PLASMA PROTEINS IN NORMAL PERSONS

We examined the plasma proteins of nine normal medical students and physicians. Our analyses of the content of total protein, of serum albumin, of serum globulin, and of fibrin in the blood plasma of these nine normal persons ranging in age between 20 and 40 years has resulted in figures that are in good agreement with the figures obtained by all recent investigators. We have calculated the arithmetic mean and the coefficient of deviation for total protein, serum albumin and serum globulin from the values obtained by Linder, Lundsgaard and Van Slyke² on seven normal persons, by Epstein⁵ on seven normal persons, and by ourselves on nine normal persons. These figures are shown in table 1. The "mean" of our nine values corresponds very nicely with the mean from the twenty-three values obtained by the investigators. The differences between our "means" and the "means" calculated from all the values is less than the coefficient of deviation in

4 Wu, H. J. Biol. Chem. 51:33 (March) 1922.

5 Epstein. Contribution to the Study of the Chemistry of Blood Serum, J. Exper. Med. 16:719, 1912; Further Studies on the Chemistry of Blood Serum, ibid. 17:444, 1913.

every case Peters⁶ has shown that these values obtained on oxalated plasma are 6 per cent lower than in nonoxalated plasma because of the contraction in erythrocytes brought about by the oxalate. As all determinations on plasma will be carried out on oxalated plasma there is no need for applying this slight correction. Values of total plasma protein less than 6 and more than 8.5 should be looked on as being outside the range of normal. A serum albumin content less than 3.5 or greater than 5.5 should be considered outside the normal range. A plasma containing less than 1.5 Gm. of serum globulin or more than 3.5 Gm. per hundred cubic centimeters is certainly outside the normal range. In fact, when the serum globulin content of the plasma in a case of nephritis is below 2 there is reason to believe that the globulin content has diminished from the normal value and when the globulin is found higher than 3 in a case of nephritis there is good ground for suspicion that the globulin content has increased above the normal value for that case.

The results of our investigation of the plasma proteins in ten cases of acute and subacute glomerulonephritis are contained in table 2. Seven cases showed definite lowering of the total protein content of the plasma. This lowering was due largely to the reduction in serum albumin content. The serum albumin in case 1 is only 33 per cent of our mean normal value. In cases 2 and 3 the serum albumin is only 40 per cent of our mean normal value. On the whole there is little tendency for the serum globulin values to fall, in fact, in cases 4 and 10 the values for serum globulin are higher than any of the values in Linder, Lunds-gaard and Van Slyke's or our normal cases. There is no reduction in the amount of fibrin in any case, and cases 8, 1 and 2 show definite increases above what may be considered normal values. We neglected making quantitative determinations of the daily output of plasma proteins in the urine so that our work throws no light on the source of loss of plasma protein. Qualitative tests always showed heavy traces of albumin in the urine when the plasma proteins were lowered. There is unquestionably a close inverse correlation between degree of edema and amount of plasma protein or even better between degree of edema and amount of serum albumin. But this inverse correlation should not be assumed to prove a cause and effect relation between reduction in plasma protein and edema, because a case of acute glomerulonephritis may have lowered plasma proteins at a time when diuresis is in process and all visible edema has disappeared or a case of acute glomerulonephritis may show no reduction in plasma protein and yet a very marked edema be visible. Patient 4 came into the hospital with moderate edema which disappeared within two weeks on fluid restriction. At the

⁶ Peters, J. P., Eisenman, A. J., and Bulger, H. A. *J. Clin. Investigation* 1: 435 (June) 1925.

TABLE 2—*Acute and Subacute Glomerulonephritis*

Case	Albumin	Globulin	Albumin		Total	Remarks
			Globulin	Fibrin		
1	16	36	0.45		52	First determination at time when edema was very marked, eye-grounds showed edema of nerve head and surrounding retina, urine albumin, heavy trace
	19	29	0.7	0.7	48	Second examination at time when edema, which had previously disappeared, had reappeared—6 weeks after first determination—acute nephritis probably going on to chronic nephritis
2 (Sept.)	23	18		Lost	46?	Extreme grade of anasarca, severe ascites and mild hydrothorax which largely disappeared on fluid restriction and ammonium chloride administration, albumin, 4 plus
Ascites	0.6	0.4		Trace		
Anasarca	0.08	0.0		0.012		
(Nov.)	20	16	1.3	0.6	36	Second entrance, albumin, 4 plus, extreme grade of anasarca, severe ascites and hydrothorax, anasarca fluid flowed from Southey tubes under pressure of 10 cm. of water, necropsy showed subacute glomerulonephritis, osmotic pressure of plasma against anasarca fluid at 37°C was 10 mm. of mercury—normal is 22 mm.—as measured by us
Hydrothorax fluid	0.5	0.1		Trace		
Anasarca	0.07	0.0		0.013		
3	20	21	1.0	0.3	41	Subacute glomerulonephritis confirmed by postmortem examination, marked edema, urine showed heavy trace of albumin
4	25 (March 26)	31	0.8	0.4	56	Subacute glomerulonephritis with healing, urine showed ++ albumin up to June, then +, in July faint trace, Volhard water test, May 19, 1,215 cc. output in 4 hours, specific gravity, 1.002 at point of greatest dilution, at this time serum albumin below normal, moderate diuresis started about April 4 and visible edema had disappeared before May 7, Volhard test, May 3, showed 850 cc. output in 4 hours on 1,100 cc. intake
	29 (May 7)	30	1.0	0.3	59	
	35 (June 11)	34	1.0	0.4	69	
	49 (July 3)	32	1.5	0.4	81	
5	25 (1st)	23	1.1		48	Acute nephritis, edema present at first determination, albumin 4+
	40 (2d)	18			58	Second determination edema no longer visible but albumin + in urine, this determination 3 weeks after first, on 30 Gm. protein per day in diet
6	26	29	0.9	0.4	55	Acute nephritis, moderate edema and oliguria at time determination was made, diuresis started 7 days after determination was made, urine showed heavy trace of albumin
7	42 (1st)	28	1.5	0.4	70	Acute nephritis, mild edema of face and ankles and lung edema and hydrothorax at time of first determination, trace of albumin in urine
	31 (2d)	16	2.0	Lost	51?	Visible edema cleared up at time of this determination, diuresis had set in, blood pressure nearly normal
8	40	26	1.5	0.6	66	Acute nephritis, no edema demonstrable at time of determination, blood urea nitrogen 70, faint trace of albumin in urine
9	42	26	1.6	0.4	68	No edema visible, urine showed only a faint trace of albumin
10	52	32	1.6		84	Acute nephritis, markedly edematous at time of determination, but blood pressure had dropped to normal, phenolsulphonphthalein, which had been 20% on entrance, was 45% 1 week before this determination and 2 weeks after onset, and diuresis was well under way at this time, the case was a very acute one with rapid recovery, Esbach 0.1% and output of urine 400 cc. shortly after entrance

same time the blood showed a definite reduction of plasma proteins, the serum albumin on May 7 being 60 per cent of our mean normal at a time when there was no visible edema nor any evidence of "concealed" edema. A Volhard water excretion test² performed May 3 demonstrated that these kidneys could excrete at least 5 liters per day under stress. Case 7 showed a normal plasma protein content at a time when visible edema was present and a slightly reduced plasma protein content after all visible edema had disappeared. The plasma protein and serum albumin content of case 10 were normal at the time when there was marked visible edema present.

In table 2, case 2, we have added analyses of hydrothorax fluid, ascites and anasarca fluid. On one occasion 6,000 cc of ascites and on another occasion 1,500 cc of hydrothorax fluid were withdrawn from this patient, representing 36 Gm of serum albumin and 24 Gm of serum globulin in the ascites fluid withdrawn and 7.5 Gm of serum albumin and 1.5 Gm of serum globulin in the hydrothoracic fluid withdrawn. There was an indeterminate amount of ascites and hydrothoracic fluid remaining after the tapping so that we can be sure of a loss of more than 45 Gm of serum albumin and 25 Gm of serum globulin in these fluids. The protein content of the anasarca fluid was very small and in spite of the large amount of anasarca fluid can have played little part in the loss of serum albumin from the blood plasma. The total serum albumin content of both the ascites and hydrothorax fluids was approximately 25 per cent of the total plasma serum albumin content. The serum albumin in the ascites and hydrothoracic fluids can therefore account for a small part of the serum albumin loss from the plasma. Patient 2 weighed about 180 pounds (81.6 Kg) and therefore his plasma volume was about 4,000 cc.⁷

Four thousand cubic centimeters of normal plasma contain about 80 Gm of serum globulin. Four thousand cubic centimeters of plasma from patient 2 contained about 40 Gm of serum globulin. There had therefore been a loss of about 40 Gm of serum globulin from the plasma. The amount of serum globulin in the ascites and hydrothoracic fluid in patient 2 might account for the greater part of the loss of serum globulin from the plasma. It will, of course, be impossible to state whether the protein lost into the ascites and hydrothoracic fluids is a factor of any consequence in the reduction of serum albumin and globulin in the plasma of patients suffering from nephritis until quantitative studies on the rate of regeneration of serum albumin and globulin and the rate of loss in the urine have been made. All our patients with nephritis were on a diet containing only 30-35 Gm of protein per day.

⁷ Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E. G. Changes in the Volume of Plasma in Nephritis, *J. Exper. Med.* **39**: 921 (June) 1924.

TABLE 3—*Chronic Glomerulonephritis*

Case	Albu min	Glob ulin	Albumin		Total	Remarks
			Globulin	Fibrin		
11	18	32	05	03	50	No visible edema at time proteins were determined, but there was a marked diuresis going on, with 600 cc intake, output from 1,400 to 2,400 cc per day, Volhard water test, 600 cc output in 4 hours, lowest specific gravity, 1.008, could not concentrate above 1.015, stage 2 of Volhard and Fahr, albumin in urine +++++
12	21	28	08	05	49	Moderate anasarca and ascites, stage 2 of Volhard and Fahr, albumin +++++, Volhard water test showed 780 cc output in 4 hours, with 1500 cc intake, lowest specific gravity, 1.007, not able to concentrate beyond 1.015
13	21	35	06	13	56	History of nephritis for 6 years before entrance, face and eyelids slightly puffy, slight edema of ankles no ascites or hydrothorax, postmortem examination revealed chronic glomerulonephritis no arteriosclerosis, coarsely granular kidneys eyegrounds showed edema of disk and retina cotton wool spots and hemorrhages, stage 3 Volhard and Fahr
14	30	25	12	03	55	No edema present at this time but 2 months previously edema was marked, probably stage 2 of Volhard and Fahr, Volhard water test showed lag in rate of excretion, inability to dilute below 1.004
15	30 (Jan 23)	26	12	04	56	At time of entrance stage 1 according to Volhard and Fahr, going into stage 2 during 9 months' hospital stay, January 23, marked edema of legs and some swelling of eyelids and face, on restricted fluid (500 cc per day) edema disappeared in few days but Volhard water test always showed reduced velocity of water excretion and inability to dilute below 1.004, also inability to concentrate beyond 1.015 specific gravity, secondary anemia slowly developed, no retention of nitrogenous metabolites albumin in urine, 0.7% (Esbach) at entrance, output 7 Gm per day, rapidly decreased to 0.2% (Esbach) and 2 Gm per day output
	33 (Feb 6)	25	13	05	58	
	34 (March 6)	25	14	05	59	
	34 (April 14)	23	15	05	57	
16	25 (March 2)	26	10	05	51	Second stage according to Volhard and Fahr, moderate edema of legs, February 28, on entrance, disappearing rapidly on restricted fluid (500 cc per day), no edema present March 2, diuresis of 1,400 to 2,400 cc per day from February 28 on, Volhard water test March 12, 1,100 cc output in 4 hours, lowest specific gravity, 1.004 not able to concentrate above 1.015, 0.05% albumin (Esbach) in urine, 1/2 to 3/4 Gm output per day, 170 mg cholesterol per 100 cc plasma
	30 (March 13)	24	13	04	54	
	37 (April 25)	24	15	04	61	
17	42	32	13	03	74	Very slight edema of ankles only, clinically corresponded to stage 3 of Volhard and Fahr
18	50	25	20	03	75	Albumin in urine, 0.1% (Esbach), daily output 1 Gm (Esbach), puffiness of face, slight edema of extremities stage 2 of Volhard and Fahr
19	51	26	20	03	77	Both heart failure and marked renal insufficiency present, edema of extremities and hydrothorax, average output of protein in urine was 2.7 Gm per day for 15 days (Esbach method), total loss protein in urine in 15 days equaled 41 Gm, loss of protein from blood plasma equaled 39 Gm, patient received 30 Gm protein per day in food eyegrounds showed papilledema, narrowed arteries, a few "hard" white spots in maculae one small cotton wool spot and a few flame shaped hemorrhages, necropsy revealed chronic glomerulonephritis (third stage) with moderate degree of arteriosclerosis of small vessels of kidney and passive congestion of liver
	Fourteen days later 46	20		04	66	

PLASMA PROTEINS IN CHRONIC GLOMERULONEPHRITIS

If we now look at table 3, in which the results of our analyses of the serum proteins in chronic glomerulonephritis are tabulated, we see that here also there is a tendency to reduction in the plasma proteins, especially in the serum albumin content. The correlation between reduction in plasma protein and amount of visible edema is not so good in these cases as in the acute and subacute cases of table 2. Case 11 shows a fall in total plasma protein to 70 per cent of the normal and a decided fall in serum albumin to 35 per cent of the normal, yet there was no visible edema at the time the blood was drawn for chemical analysis. The Volhard water test, however, shows that there was a decided lag in rate of output of water and inability to dilute to "normal" values. In other words, there was a tendency to edema formation which was only checked by a restricted water intake. Case 18 shows a normal plasma protein content and normal serum albumin content with mild edema. In this case the daily output of protein in the urine is only 1 Gm. Case 17 also shows edema formation with normal plasma protein concentration. The serum albumin concentration in the plasma is within the limits of the values obtained in normal persons. In neither of these cases was there any symptom or sign pointing to heart failure as a cause of the edema. Case 14 shows a reduction in total plasma proteins to 80 per cent of our mean normal and a reduction in serum albumin to 60 per cent of our mean normal with no edema present at the time the blood was withdrawn for analysis. In this case there was a tendency to edema formation which was held in check by water restriction. Case 15 shows low plasma protein content with marked edema which disappeared on fluid restriction. But the water excretion test showed decreased ability to excrete water and we can be sure that edema would have been present if the fluid intake had not been kept down to 500 cc per day. Case 16 had edema on entrance but this had disappeared by the time the blood was first withdrawn for analysis because of fluid restriction. Water excretion tests showed mildly reduced rate of water excretion. Case 19 showed marked edema with normal plasma protein and normal serum albumin content. But this patient showed a markedly dilated heart and a large passive congested liver so that the edema might be considered as largely due to heart failure. On the whole the correlation between reduction in plasma protein and reduction in rate of water excretion under the stress of a "peak" load is better than that between reduction in plasma protein and visible edema.

PLASMA PROTEIN CONCENTRATION IN CHRONIC NEPHROSIS

The three cases of chronic nephrosis of table 4 showed a marked reduction in total plasma protein. This reduction was due largely to the reduced serum albumin content. The globulin content is nearly

normal and the fibrin content somewhat elevated. All three patients showed edema of marked degree on entrance. In case 20 the edema was very slight after the patient had been two and one-half months in the hospital on first entrance. At times there was an output of 1,500-1,800 cc of urine per day with only 700-800 cc intake. The patient was kept in bed and put on low protein diet. Following a tonsillectomy

TABLE 4—*Chronic Nephrosis*

Case	Albumin	Globulin	Albumin		Total	Remarks
			Globulin	Fibrin		
20	18 (1st) Dec 5	22	08	03	40	On first entrance to hospital, September, 1923, patient exhibited marked anasarca, hydrothorax and ascites, blood pressure, 110 systolic, 70 diastolic, albumin, 6 Gm per liter on entrance, in December, slight trace only, phenolsulphonphthalein, 60% in 2 hours, marked edema and oliguria (600 cc) at time blood was withdrawn for analysis.
(2d)	19 (July 3)	31	06	07	50	Second entrance to hospital, extreme grade of anasarca, ascites and hydrothorax, ascites looked like soap water, urine output 200 to 300 cc on entrance, weight, 215 pounds (97.5 Kg) on June 16 entrance, weight, 144 pounds (65.3 Kg) August 15, 71 pounds (32.2 Kg) of water lost, diuresis started about July 10, the output per day being between 1,000 and 2,000 cc, by July 22 the output was daily between 2,000 and 3,000 cc, it remained at this level until August when it was between 1,500 and 2,000 cc until about August 15 when it was between 1,000 and 1,500 cc, in September patient left hospital, Volhard water test showed 90% normal output, August 4, daily output of albumin in urine, 4 to 5 Gm (Esbach) even in September, always heavy trace in urine, was on diet containing 200 Gm proteins per day after July 1, was on 30 Gm previously, fibrin determination of August 14 lost, globulin determined on fibrin-free filtrate and 0.6 fibrin value added, the error will not be over 0.2.
	20 (July 23)	33	06	06	53	Came in with very moderate anasarca and ascites, increased during 4 weeks in hospital so that weight was increased 20 pounds (9 Kg), during hospital stay received 200 Gm protein per day, albumin in urine 0.3% by Esbach, measured only on one occasion, between 2 and 3 Gm loss of protein in urine on this day, during hospital stay always heavy trace.
	23 (Aug 14)	23?	10	Lost	46?	
	23 (Aug 22)	18	13	04	41	
	28 (Sept 4)	14	20	02	42	
21	17 (Dec 2)	17	10	04	34	Has had periods of anasarca and ascites off and on for 4 years, albumin (Esbach) in urine 2 to 5 Gm per day, average about 2.8 Gm, patient was child weighing 35 Kg.
	14 (Dec 27)	31	05	06	45	
22	25	16	16	03	41	

in January, 1924, the daily output of urine was less. The patient was allowed to go home early in February. He returned to the hospital, June 16, 1924, with a most extreme grade of edema. We calculated that his body had accumulated about 30 liters of fluid above its normal water content. He was again put on a restricted fluid intake (500 cc), rest in bed, and a low protein (30 Gm) diet. After July 1, when the medical services were changed, he was given a diet of 200 Gm of pro-

tein per day, and was kept on this diet until discharge, about September 5. We did not control the amount of protein actually eaten but no one ever saw any of his food returned and he asserted that he not only ate all of his food but enjoyed it. He had never been able to get all the meat he wanted before in his life and he was now enjoying it immensely. His body had probably suffered a large protein loss on the previous diet and was now storing it up. Diuresis set in shortly after going on the high protein diet. This diuresis was at its maximum at a time when the total plasma proteins were 75 per cent of the mean normal value and when the serum albumin content was 40 per cent of the mean value as found in our normal persons. Therefore, a most marked diuresis is possible at a time when the proteins and especially the serum albumin concentration in the plasma are very low. With a plasma protein content 75 per cent of the mean normal and the serum albumin content less than 50 per cent of our mean normal value this patient was able to put out 1,350 cc of urine in four hours after drinking 1,500 cc. This experiment seems to indicate that the reduction in serum albumin and protein content in the blood plasma is only a minor factor in edema formation in the nephropathies. It will also be noted that the fibrin content is high and the albumin-globulin ratio low at a time when diuresis is good and when a Volhard water test shows excellent ability to excrete urine.

PLASMA PROTEIN CONCENTRATION HYPERPIESIA WITH HEART FAILURE

Edema formation in this disease is only of considerable degree when heart failure develops. For this reason we only investigated the plasma protein content in cases of hyperpiesia with heart failure. In the few cases that go on to renal insufficiency the urine shows hyposthenuria and the Volhard water test shows that the rate of water excretion is decidedly reduced but the rate is sufficient for a daily output of from 2 to 3 liters and for this reason edema formation is rarely found when there is no heart failure.

Three out of four of our cases of hyperpiesia in the heart failure stage showed definite reduction of the total amount of plasma protein. A 50 per cent reduction of the serum albumin was alone responsible for this because the globulin was not reduced. Case 23 showed marked edema at the time of the withdrawal of the blood for this analysis. A few weeks later the edema had disappeared on fluid restriction and digitalis medication. Case 23 showed a great reduction in serum albumin with apparently no loss of protein in the urine. Qualitative tests on five different occasions showed no protein in the urine. The loss of protein in the hydrothorax and ascites might account for it if their serum albumin content corresponds to that found in the hydrothorax

in case 26 But if loss of serum albumin could be accounted for through loss in these fluids we should expect to find a like loss of serum globulin from the blood due to the same mechanism or, otherwise, we must assume the hydrothoracic and ascitic fluids had a high serum albumin content and low globulin content We cannot settle this question without globulin and albumin determinations in these fluids Possibly the severe liver damage in this case had some relation to the reduction in the amount of serum albumin in this case Necropsy revealed a severe degree of Laennec's cirrhosis On the other hand, one case of Laennec's cirrhosis with marked edema studied by us showed normal plasma proteins Case 24 showed marked reduction of serum albumin (50 per cent) with

TABLE 5—*Hyperpiesia in Heart Failure Stage*

Case	Albumin	Globulin	Albumin		Total	Remarks
			Globulin	Fibrin		
23	2.5	3.2	0.8	0.2	5.7	Urine showed no albumin on five occasions, protein not restricted in diet, marked cirrhosis of liver with damage to large percentage of liver cells and hypertension heart revealed by necropsy, no renal pathology of note, marked ascites, edema and hydrothorax
24	2.5	2.3	1.1	0.3	5.7	Esbach showed only trace of albumin, marked anasarca, hydrothorax and ascites, necropsy revealed hypertension heart, marked chronic passive congested liver and very mild degree of arteriolar sclerosis of kidney
25	2.6	3.3	0.8	0.3	5.9	Albumin two and three plus in urine, marked ascites and hydrothorax, moderate anasarca, necropsy revealed hypertension heart, moderate degree of arteriolar sclerosis of kidney and marked passive congestion of liver
Hydrothorax fluid	0.8	Trace		Trace		
26	4.2	3.2	1.3	0.2	7.4	Urine showed heavy cloud of albumin, marked ascites and hydrothorax, moderate anasarca, necropsy revealed hypertension heart, mild coronary sclerosis, very mild degree of arteriolar sclerosis of kidney, moderate degree passive congestion of liver
Hydrothorax fluid	1.7	1.6		Trace		

only a trace of albumin in the urine Here also loss of serum albumin in the urine does not account for the reduction in serum albumin content of the plasma Cases 25 and 26 showed heavy traces of albumin in the urine but case 26 showed no reduction in serum albumin or, at the most, a very mild one, and case 24 showed no more reduction than the cases in which there was no protein or very little protein loss in the urine It may be of significance that three cases showing marked reduction in serum albumin content of the plasma all had severe liver damage whereas the case showing little or no reduction in serum albumin in the plasma only showed a moderate passive congestion of the liver

COMMENT

When we come to examine the protein content of the blood plasma in acute and chronic glomerulonephritis we find that the total content is definitely reduced in 70 per cent of our nineteen cases and that this reduction is largely due to the diminution in serum albumin. In this our figures agree well with those of Epstein,⁸ with those of Rowe,⁹ with those of Limbeck and Pick,¹⁰ and with the results of Linder, Lundsgaard and Van Slyke.²

Kahn's¹¹ investigation revealed much smaller reductions and they were of less frequent occurrence. The globulin content is only occasionally slightly reduced. It is occasionally increased, though in general it is within the normal range. The fibrin content of the plasma is on the whole slightly elevated.

The first question that arises is as to the mechanism of the loss. Linder, Lundsgaard and Van Slyke² have shown that the total quantity of plasma is not increased in glomerulonephritis unless there is a severe secondary anemia of long standing. Only case 13 of our series had an anemia of such a degree as would cause an appreciable increase in total plasma volume. But the degree of reduction in albumin is greater than any known increase in total plasma with the severest secondary anemia. Moreover, if hydiemic plethora were a factor in reducing the percentage content of plasma proteins there would be an equal reduction in the content of albumin and globulin. But the serum albumin is reduced to 45 per cent of the mean normal whereas the globulin is increased to 135 per cent of its mean normal value even in our case 13, in which there is some probability of a 20-30 per cent increase in total blood plasma. In other words, neither the degree of reduction of serum albumin nor the fact that the serum albumin is reduced and the globulin is increased can be explained by hydiemic plethora. There is a slight increase in total plasma during diuresis as Linder, Lundsgaard and Van Slyke² have shown and as we ourselves have frequently observed but this is of a different order of magnitude from the degree of reduction in serum albumin and need not be considered in a discussion as to the cause of reduction in serum albumin in the blood plasma in nephritis.

All our patients with nephritis showing definite reduction in the total protein content of the plasma had severe albuminuria and the next

8 Epstein. Contribution to the Study of the Chemistry of Blood Serum, *J. Exper. Med.* **16** 719, 1912.

9 Rowe. Refractometric Studies of Serum Proteins in Nephritis, *Arch. Int. Med.* **19** 354 (March) 1917.

10 Limbeck and Pick. Ueber die Quantitativen Verhaeltnisse der Eiweisskorper in Kranken, *Prag. med. Wchnschr.* **18** 133, 1893.

11 Kahn. Protein and Lipin Content of Serum in Nephritides, *Arch. Int. Med.* **25** 112 (Jan.) 1920.

thought that arises is as to the relation of loss of protein in the urine to loss of protein from the plasma Epstein¹² has maintained that the reduction in plasma proteins is due to their loss in the urine Our observations in case 19 seems to substantiate Epstein's contention This patient had twelve determinations of the total protein in his urine for twelve days by the Esbach method His average loss of protein in the urine per day was 2.7 Gm The total loss of protein in the urine during fifteen days was therefore 41 Gm The first determination of plasma protein content was made four days after entrance to the hospital, at which time the total plasma protein was 7.7 Gm per hundred cubic centimeters Fifteen days later it was 6.6 Gm per hundred cubic centimeters The patient's weight according to the actuarial tables of 1912 was 60 Kg There were 3,000,000 erythrocytes per cubic millimeter of blood Linder, Lundsgaard and Van Slyke² have shown that the plasma content in patients with nephropathies and an erythrocyte count around 3,000,000 is approximately 6 per cent Therefore, our patient had 3,500 cc of blood plasma As the protein content of each 100 cc of plasma was reduced 1.1 Gm the total protein loss from the plasma was 39 Gm This loss of 39 Gm of protein from the plasma corresponds well with the 41 Gm of protein lost in the urine Although we are ready to believe that the greater part of the loss in protein from the plasma is due to the albuminuria, nevertheless, we are unwilling to believe that no other factors are playing a part in the changes in protein content of the plasma Not infrequently there is an increase in globulin at the same time that there is a marked decrease in serum albumin Moreover, Linder, Lundsgaard and Van Slyke¹³ have had one case in which there was an average daily loss of protein in the urine of 6 Gm over a period of four months with hardly any change in the albumin and globulin content of the plasma It is necessary that some one should carefully determine the albumin and globulin losses in the urine over many days in conjunction with a determination of the plasma proteins in order to settle the question quantitatively as to the relation of loss of protein in the urine to loss of protein from the plasma

Epstein¹² has contended that a low protein content of the plasma in nephritis was the cause of edema and that by feeding a high protein diet the protein content of the plasma would increase and the edema be caused to disappear Our observations show that as a rule low protein content is associated with edema, and that as the protein content increases as a rule diuresis sets in and the edema decreases On the other hand, our figures do not show that the edema is dependent to

12 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, *Am J M Sc* **154** 638 (Nov) 1917, Further Observations on the Nature and Treatment of Chronic Nephrosis, *ibid* **163** 167 (Feb) 1922

13 Linder, Lundsgaard and Van Slyke (reference 2, case 8)

any great extent on the low protein content, for cases 4, 11, 14, 15 and 16 all showed reduced total protein with marked reduction of the serum albumin content of the plasma at a time when diuresis had set in and edema had disappeared. Moreover, cases 10, 17 and 18 are examples of nephritis with edema and normal plasma protein content and normal serum albumin contents and no signs suggestive of heart failure. Now it is possible to have a tendency to edema and yet no edema formation because of water restriction. For example, case 11 showed no edema at a time when the plasma proteins were reduced to 70 per cent of the mean normal and the serum albumin reduced to 40 per cent of the mean normal. But in this case there was a water restriction to 600 cc of fluid per day. The Volhard water test done on this patient at this time showed that there was a marked lag in excretion of a peak load, yet there was no visible edema and a definite diuresis under these conditions. Patient 11 with no visible edema and good diuresis on an intake of 600 cc of fluid had less serum albumin and only slightly more total protein in the plasma than patient 2 in whom a most extreme grade of edema was always present even on an intake of less than 500 cc of fluid per day. Much more work is necessary to clear up the relation of plasma protein content to formation of edema and rate of water excretion. Certainly quantitative determinations of the total amount of protein in the plasma and of the serum albumin content show that reduction in amount is not necessary for edema formation and that good diuresis is possible with marked reduction. Our observations do not show a completely normal output of water under a Volhard test when the plasma proteins, especially the serum albumin content, are low. But some of the values obtained were nearly normal, i. e., 80-85 per cent of the peak load output of normals. We are therefore inclined to believe that though the plasma protein reduction tends to slow up water output somewhat, yet it is really only a minor factor in edema formation.

All three of our cases of chronic nephrosis showed a marked reduction in total protein of the plasma. The reduction in the serum albumin was most marked, the serum globulin being slightly reduced in a few instances but also increased slightly in three examinations. The fibrin was definitely increased in the plasma of two of these cases, these being the cases that showed slightly increased globulin so that part of the globulin increase was due to increased fibrin. All three cases of chronic nephrosis showed anasarca and ascites and one can find a good correlation between edema and low plasma protein in chronic nephrosis. On the other hand, correlation does not mean a cause and effect relationship between two variables. If we take case 20 for an example, we find the patient entering the hospital with most extreme edema—70 pounds (31.8 Kg) of water—and showing total plasma proteins 70 per cent of the mean normal and serum albumin 40 per cent of the normal mean.

On entrance the daily output of urine was between 200 and 300 cc. About three weeks after entrance diuresis started and continually increased in amount until only five weeks after entrance there was a daily output of 2,000-3,000 cc of urine on an intake of only 800 cc of fluid. During this period of diuresis the total proteins of the plasma were low, 60-75 per cent of the normal mean and the serum albumin was from 45-50 per cent of the mean normal. There can therefore be marked diuresis and disappearance of edema with markedly reduced serum albumin and total protein content of the plasma. The Volhard water test always showed some lag in the excretion of water in these cases when the serum albumin and total protein in the plasma were low but, August 4, when proteins were very low, the patient put out 1,300 cc of urine in four hours after drinking 1,500 cc. This is close to the normal output. At this period the patient was putting out daily about 800 cc more urine than the fluid intake. From this experiment we concluded that the patient could not take care of a peak load of water in a quite normal manner but could have a diuresis of 1,500-2,000 cc of urine on an 800 cc intake. We conclude nothing as to the rôle of the plasma proteins excepting that their rôle is a very minor one in diuresis and in the handling of a peak load of water.

Patient 20 received 200 Gm of protein per day in his diet after July 1. There was no check made of the food returned but he stated that he ate every bit and we are inclined to believe that he did eat this large amount of protein every day. On this diet the total protein content of the plasma seems not to have increased, rather to have decreased slightly. The globulins seem to have decreased very much on this diet, whereas the serum albumin increased from a value about 40 per cent of the mean normal to a value about 55 per cent of the mean normal in two months. This isolated experiment proves only that a case of nephrosis may show no increase in total protein content of the plasma on a high protein diet over many weeks.

The fibrin content of the plasma is high during edema but it is also high after diuresis has started and there is no evidence in our figures that it has a causal relation to the edema formation. Case 21, indeed, showed edema and normal fibrin. There is no evidence in our figures for Rusznyak's¹⁴ contention that increased fibrin content is a prominent factor in the causation of edema in nephritis for some cases with edema had normal fibrin content in the plasma and some cases in which edema was disappearing or had disappeared showed increased fibrin content.

Linder, Lundsgaard and Van Slyke² have shown that in nephrosclerosis, the disease that we have termed hyperpiesia, there is no appar-

¹⁴ Rusznyak, S. Untersuchungen ueber die Entstehung des Oedems bei Nierenkranken, *Ztschr f d ges exper Med* **41** 532, 1924.

ent change in the plasma protein content. One of their patients had edema with myocardial insufficiency and showed a slight drop in serum albumin content. Three of our four cases of hyperpiesia with heart failure showed reductions in total protein of the plasma below the lowest limit of normal and reduction of serum albumin to about 55 per cent of the mean normal value. It is remarkable that in case 23 proteinuria was not present on any of the five occasions when qualitative tests were made on his urine. Evidently it is possible to have a marked reduction in serum albumin without loss of protein in the urine. In other words, metabolic and other processes may be the cause of changes in the serum albumin content of the plasma. The liver parenchyma was badly damaged in this case by atrophic cirrhosis and we wonder whether disturbance of liver function may not have had something to do with the reduction in serum albumin content of his plasma. In case 24, also, the loss of protein in the urine was slight and yet there was a reduction in the serum albumin to one-half our mean normal value.

We began this investigation to find out what part the osmotic pressure of the colloids of the plasma might play in edema formation, on the assumption that the osmotic pressure of the colloids of the plasma was a simple straight line function of their concentration. Now this assumption is not true for not only the concentration of the various hydrophilic colloids determines their osmotic activity but their state of dispersion and hydration play an important part in this activity. Moreover, the Donnan equilibrium between the cations and anions in the plasma and the ultrafiltrate outside the capillaries might be such as to facilitate ultrafiltration under edema conditions. Our studies would indicate that the osmotic pressure of the colloids of the plasma play a very minor rôle in edema formation if this osmotic pressure is a simple function of the concentration of these colloids. It is now necessary to study the osmotic pressure of the plasma directly and to correlate it with edema formation, diuresis and "peak" load tests for water excretion in various stages of edema formation and disappearance in order to evaluate the true significance of colloid osmotic pressure for edema formation and diuresis. The studies of Schade and Claussen¹⁵ and of Govaerts¹⁶ on osmotic pressure in nephritis throw no light on the significance of osmotic pressure for edema formation because they do not include determinations of osmotic pressure throughout the course of edema formation and disappearance and are not accompanied by water function tests. Until more systematic and better controlled investi-

15 Schade, H., and Claussen, F. Der Onkotische Druck des Blutplasmas und die Entstehung der renal bedingten Oedeme, *Ztschr f klin Med* **100** 363, 1924

16 Govaerts, P. Etude clinique de la Pression osmotique des Proteins du serum dans la Pathogenie des oedemes, *Compt rend Soc de biol* **91** 116 (June 20) 1924

gations are made the problem of colloid osmotic pressure in its relation to edema formation cannot be considered solved

SUMMARY

1 In glomerulonephritis there is a tendency to a reduction in the total protein content of the plasma

2 This reduction is due largely to decrease in serum albumin content. Serum globulin content may rise slightly at the same time that serum albumin falls

3 The reduction in protein content of the plasma is usually correlated with marked loss of protein in the urine, and is probably largely due to loss in the urine. In one case of chronic glomerulonephritis the total protein lost from the urine in fifteen days was nearly equal to the total protein found in the urine during the same fifteen days. At the same time one case of hyperpiesia with heart failure showed a reduction of protein in the plasma with apparently no protein or very little lost in the urine. Therefore metabolic processes are to be considered as possible sources of loss of plasma protein

4 High protein (200 Gm per day) feeding may not cause the protein content in the blood to rise more than very slowly

5 Although reduction in protein content, especially in serum albumin content of the plasma, is frequently associated with marked edema, and although marked edema is frequently associated with low protein content of the plasma yet low protein content is not in any sense a prominent factor in producing the edema, for cases of nephritis may develop edema before the protein content of the plasma has fallen below the normal range, and with reduced total and markedly reduced serum albumin content of the plasma abundant diuresis may be going on

6 In order to evaluate the significance of the osmotic pressure of the colloids for edema formation in nephritis it will be necessary to study the relation of this pressure measured directly during the course of edema formation and disappearance and under experimental control

THE COMBINING POWER OF PROTEINS WITH ROSE BENGAL

II APPLICATION AS A QUANTITATIVE TEST ON THE SPINAL FLUID *

SANFORD M ROSENTHAL, M D

AND

F DOUGLAS ACKMAN, M D

MONTREAL, CANADA

In a previous article ¹ a method was described whereby the adsorption of rose bengal B (tetrachlorotetraiodofluorescein) on proteins could easily be determined in a quantitative way. This dye stuff attains its maximum rose color at p_H 4.8 or above, but it behaves as an indicator dye and is decolorized on adding acid, dilute aqueous solutions are practically colorless below p_H 2.2. If proteins are present the dye will combine with them in the form of its colored salt, and on bringing the acidity of the solution to p_H 2.2, that portion of the dye in combination with the proteins retains its color, while the free dye is decolorized. The color that remains on acidifying the solution therefore represents the adsorbed dye and it may be easily estimated by colorimetric comparison with a standard solution of rose bengal of known strength.

It has been shown that this is a colloidal reaction that in body fluids is primarily a function of the proteins, and that each protein possesses a characteristic degree of binding power. As a qualitative test it is extremely sensitive, albumin may be detected in dilutions of 1 to 4 millions, which is from 100 to 200 times the delicacy of the biuret or ninhydrin protein reaction ¹.

What is the nature of the combination between protein and dye? It follows the laws of adsorption, which is one of the functions of the colloidal protein particles, the quantity of dye absorbed is in part dependent on the amount of surface that the protein molecules present to the liquid in which they are suspended. The fundamental forces that govern the taking up of other substances on the surfaces of the colloidal micellae are still a subject of controversy. Reference may be made to reviews of the subject by Matthews,² Freundlich³ or Bayliss⁴. Studies

* From the department of pharmacology, McGill University, and the medical clinic, Royal Victoria Hospital.

1 Rosenthal, S. M. Studies upon the Combining Power of Proteins with Rose Bengal, *J. Pharm. & Exper. Therap.*, to be published.

2 Matthews, A. P. *Physiol. Rev.* **1**, 1921.

3 Freundlich, H. *Kapillarchemie*, Leipzig, 1923.

4 Bayliss, W. *Principles of General Physiology*, London, Longmans, Green & Co.

we have carried out indicate that the union of the dye and protein is not the result of a simple chemical reaction but that physical forces also are involved

The adsorption of rose bengal can be used as a method of study especially suited for proteins in dilute solution. In view of the increasing clinical importance of quantitative studies on the spinal fluid, it was seen fit to adapt this principle for such a purpose, especially since the information obtained from it is of a somewhat different nature from that yielded by other methods of examination now employed, and also because the simplicity of the procedure lends itself well to clinical use.

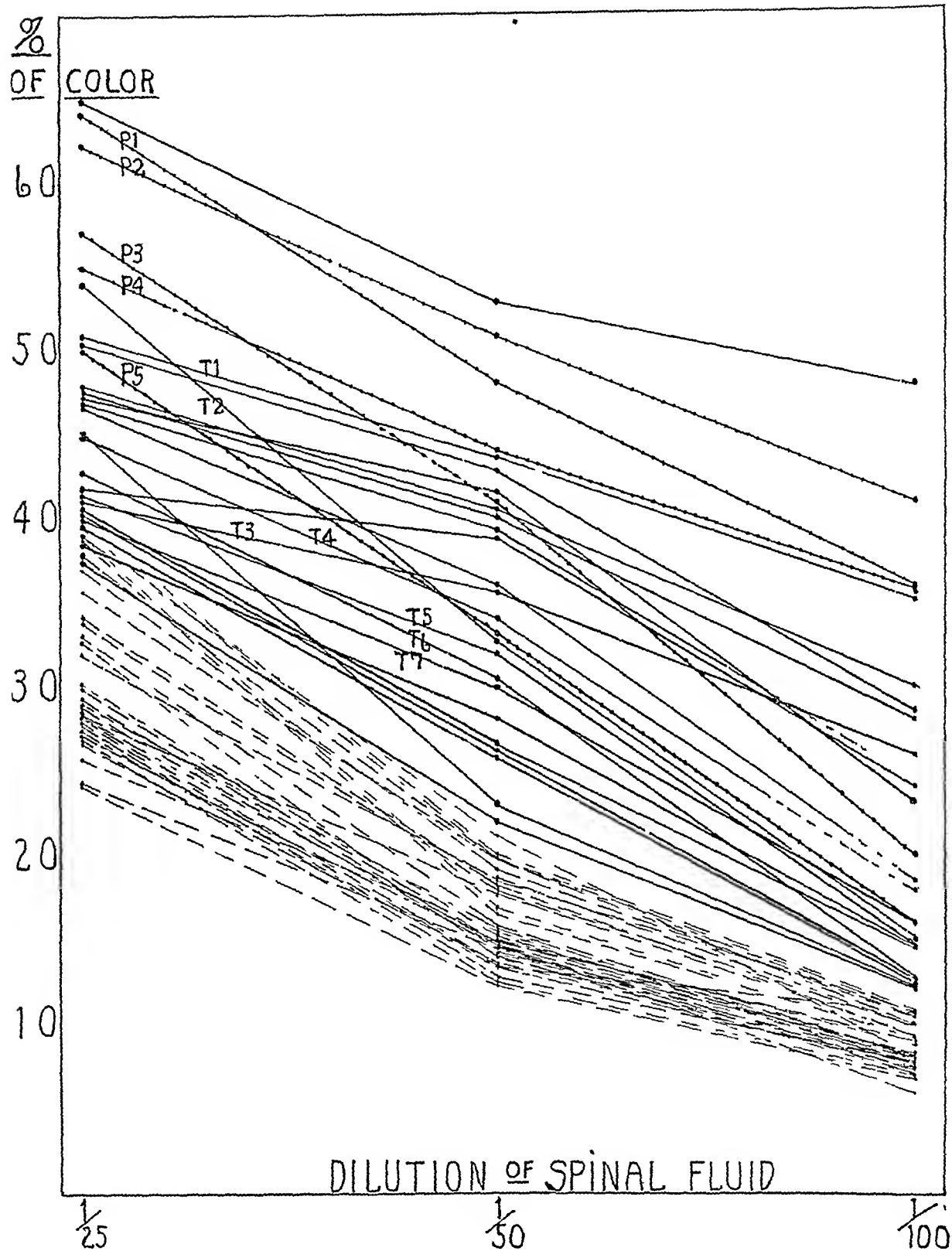
METHOD

We have shown that factors of error can be reduced to a negligible quantity by employing protein dilutions greater than 0.1 per cent. The normal protein content of the spinal fluid is only 0.025 per cent and in disease it rarely increases beyond 1 per cent. In the technic employed the lowest dilution of cerebrospinal fluid is 1:25, which in terms of protein content gives a dilution of 1:100,000 (0.001 per cent) in normal fluids. The following technic has been adopted: 1 cc of spinal fluid is diluted to 25 cc with distilled water. This is placed in four test tubes as follows:

	Tube 1	Tube 2	Tube 3	Tube 4
Quantity of 1:25 cerebrospinal fluid	10 cc	5 cc	2.5 cc	1 cc
Water	0	5 cc	7.5 cc	9 cc

To each tube 1 cc of 0.02 per cent rose bengal in aqueous solution should be added, and mixed by inverting the test tubes. To each tube 1 cc of tenth normal hydrochloric acid is now added and the solutions again mixed. Comparison of the color which remains should be made in a colorimeter with a standard prepared by adding 1 cc of 0.002 per cent rose bengal to 11 cc of water.

The p_H of the acidified solutions will be 2.01 to 2.2, at which acidity all of the free rose bengal will be decolorized, so that the color of the solution represents the bound dye. If a colorimeter is not available, a series of standards may be prepared as follows: 10 cc of 0.02 per cent rose bengal is added to 110 cc of water into which 1 drop of 10 per cent sodium hydroxide has been placed. 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 cc of this solution are placed in ten test tubes to which are added 9, 8, 7, 6, 5, 4, 3, 2, 1 and 0 cc of faintly alkalized water. They should be tightly corked and preferably sealed with paraffin. Their color will be retained for several months if kept in the dark, but they will rapidly lose color if exposed to the sunlight. These tubes represent from 10 to



Rose bengal test on spinal fluid in untreated neurosyphilis and in normal cases (dotted lines), P, general paralysis, T, tabes, the remaining curves with heavy lines represent cases of cerebrospinal syphilis, the percentage of color indicates that color which remains on acidifying the solutions of spinal fluid and dye, and represents the dye bound to proteins

100 per cent standards, satisfactory comparisons can be made with them by holding the tubes directly against a sheet of white paper or other white background

Other tests that are chiefly dependent on the protein content of the spinal fluid were simultaneously employed to see what relation the rose bengal reaction bore to them. The colloidal gold test was carried out according to the original technic of Lange. The gum mastic test was used after the modification of Cutting⁵. Refractometric indexes were determined with an Abbe refractometer fitted with heatable prisms, readings were made at a constant temperature of 25 C. Total proteins were estimated by a micro-Esbach method suggested by Levinson,⁶ while this method is not highly accurate it was found sufficiently exact for comparative purposes, as shown by the fact that normal values agreed with those obtained by other methods,⁷ and by the fact that duplicate readings made on the same specimen checked quite closely.

RESULTS

Tests were performed on thirty-three normal spinal fluids, fourteen of these were obtained from comparatively normal persons selected as controls. Results are shown in the accompanying chart (dotted lines). The curves fell within a range of variation closely analogous to the variation observed in the normal protein content. The amount of rose bengal bound by 1:25 dilution of spinal fluid averaged 31.6 per cent, by 1:50 dilution, 16 per cent, by 1:100 dilution 8.7 per cent, and by 1:250 dilutions 4.4 per cent. The values for the 250 dilution are only approximate as the color was too weak for colorimetric determinations of any accuracy. Estimations of weak color can more easily be made by direct comparison with the standard tubes described above.

Total proteins as determined by the micro-Esbach method varied normally from 0.02 to 0.035 per cent. The normal refractometric index at 25 C. varied from 1.3343 to 1.3345.

Neurosyphilis—Twenty-four cases of untreated neurosyphilis were studied. While it is unwise to generalize from so small a group we wish to point out that abnormal findings were obtained in all cases, four of five cases of general paralysis gave readings higher than those obtained in tabes and cerebrospinal syphilis (with the exception of case S-1). Tabes and cerebrospinal syphilis showed no distinguishing differences in their rose bengal reaction. Case S-1 has not been followed

5 Cutting, J. Mastic Test, J. A. M. A. **68** 1810 (June 16) 1917.

6 Levinson, A. The Cerebrospinal Fluid, St. Louis, C. V. Mosby Company, 1919.

7 Denis, W., and Ayer, J. B. Method for Quantitative Determination of Protein in Cerebrospinal Fluid, Arch. Int. Med. **36** 436 (Oct.) 1920. Ayer, J. B. and Foster, H. E. Quantitative Estimation of Total Protein in Spinal Fluid, J. A. M. A. **77** 365 (July 30) 1921.

sufficiently long to exclude early general paralysis Results in neurosyphilis are recorded in table 1 and in the accompanying chart

Meningitis—Spinal fluids from four patients with tuberculous meningitis were examined One of them (M-1) was very severe The rose bengal test gave values at the upper border or higher than those obtained in general paralysis

TABLE 1—*Comparative Results with Various Tests on the Spinal Fluid in Untreated Neurosyphilis and in Miscellaneous Diseases of the Nervous System**

Case	Diagnosis	Cells	Pandy	Total Protein	Rose Bengal				Colloidal Gold or Mastic	Refractive Index
					1 25	1 50	1 100	1 250		
P-1	General paralysis	30	++		64	48	36	15	G 0 1/2 1/2 1+1+1+1000	
P-2	General paralysis	18	++		62	51	41	17	G 0 3 44 4 3 2100	
P-3	Taboparesis	33	++		57	41	20	9	M 5 5 55 4 2 1000	
P-4	General paralysis	23	++	0.14	55	44	37	17	M 5 5 55 5 5 5310	1.3350
P-5	General paralysis	24	++		50	33	16	7	G 5 5 55 5 4 3210	1.3346
T-1	Tabes	44	+	0.075	51	44	37	21		
T-2	Tabes	45	++		54	33	15	6		
T-3	Tabes	115	++	0.11	40	36	26	13		
T-4	Tabes	18	+	0.075	44	34	18	8	M 5555421000	1.3344
T-5	Tabes	15	Trace	0.05	43	30	15	10		
T-6	Tabes with optic atrophy	61	+		40	30	16			
T-7	Tabes	82	+	0.04	38	28	15	8		
S-1	C-S syphilis	30	+++	0.23	65	53	48	33	G 0123332100	
S-2	C-S syphilis	18	+		47	43	23	11	M 4554310000	
	After treatment	4	0	0.023	44	35	17	8		
S-3	C-S syphilis	14	++	0.11	50	41	28	11	G -123321000	1.3347
S-4	C-S syphilis	139	++	0.15	47	40	28	12	M -5555432100	1.3346
S-5	C-S syphilis	7	Trace	0.03	47	39	24	11	M 1233210000	1.3347
S-6	C-S syphilis	20	++	0.1	42	39	24	11	G 4444321000	
S-7	C-S syphilis	3	0	0.04	42	31	15	9		
S-8	C-S syphilis (treated)	0	0	0.023	40	29	13	5		1.3348
S-9	C-S syphilis	55	+	0.04	41	26	14	7	G 0123321000	1.3345
S-10	C-S syphilis	12	+		41	26	12	6		
S-11	C-S syphilis	12	0		44	23	12	7		1.3345
S-12	C-S syphilis	18	+		38	26	15	10		
S-13	C-S syphilis	14	0	0.02	37	22	12	6	M 5555421000	1.3345
	After treatment	9	0	0.02	39	16	9	5	M 55321000000 G 1232100000	1.3346
M-1	Brain tumor	4	0	0.035	48	34	19	9	M 4421100000	1.3345
M-2	Brain tumor	8	0		40	23	15	10		
M-3	Brain tumor	3	0	0.02	38	21	11	5		1.3343
M-4	Cerebral hemorrhage	12	Trace		44	36	20	9		1.3347
M-5	Cerebral hemorrhage	18	+	0.032	40	33	17	7		
M-6	Xanthochromia (?), hemorrhage	6	+		44	40	22		M -2222210000	1.3348
M-7	Encephalitis	9	+		42	33	18	10		
M-8	VI nerve paralysis	4	0		39	27	15	5		
M-9	Multiple neuritis	4	0		43	34	22	11		
M-10	Disseminated sclerosis	16	+	0.04	38	23	11	5	M 55552100000	1.3345
M-11	Disseminated sclerosis	3	0		31	16	9	5	M 2100000000	1.3345
M-12	Hydrocephalus	2	0	0.02	20	9	4		M 3321100000	1.3341
	Normals	0.4	0	0.20 0.35	24 40	12 20	8 11	4 5.5	M 0000000000 M 4321100000	1.3343 1.3345

* M indicates mastic and G colloidal gold reaction

Two cases of pyogenic meningitis with only moderately pronounced changes in the spinal fluid gave higher readings than any obtained in neurosyphilis Because of the great increase in protein content in pyogenic meningitis, it is believed that the highest values will be observed in this condition

Miscellaneous Organic Nervous Diseases—Three cases of brain tumor are of interest because abnormal curves were obtained in the presence of normal cell counts and protein concentrations. A case of infantile hydrocephalus presented the only example of findings definitely below normal, here the chloride and sugar content and the refractometric index of the spinal fluid also were below normal but the total proteins and gum mastic test were within normal limits. A case of multiple neuritis gave an elevated rose bengal curve while other observations were normal, frequent changes in the spinal fluid have previously been observed to occur in this condition. Three cases of cerebral hemorrhage (without bloody fluid) gave distinctly elevated curves. The presence of blood in the spinal fluid renders the rose bengal test valueless because of the high protein content of the plasma that is introduced.

TABLE 2—Results with the Rose Bengal Test in Tuberculous and Pyogenic Meningitis

Case	Diagnosis	Cells	Pandy	Total Protein	Rose Bengal			
					1 25	1 50	1 100	1 250
M-1	Epidemic meningitis	250	++		75	71	55	46
	Treated 3 weeks	130	+	0.08	52	46	28	11
M-2	Pneumococcus meningitis*		+++		66	58	51	36
M-3	Tuberculous meningitis	980	+++		66	62	55	40
M-4	Tuberculous meningitis	220	++	0.10	62	52	43	27
M-5	Tuberculous meningitis	31	++	0.19	62	50	47	31
	1 week later	370	+	0.12	55	43	40	25
M-6	Tuberculous meningitis	160	++	0.05	60	50	36	15

* Fluid obtained postmortem

COMPARISON OF THE ROSE BENGAL REACTION WITH OTHER TESTS

Since the binding of rose bengal is primarily a function of the proteins, we were especially interested in the protein content of the spinal fluid. The normal protein is chiefly globulin but pathologic increases have been shown by Mestrezat⁸ and Kafka⁹ to be due mainly to albumin. Because albumin binds rose bengal more strongly than globulin it was anticipated that increases in combining power would often be out of proportion to increases in protein content and this was in general found to hold true. The possibility must also be borne in mind that proteins that are put forth as a result of disease differ from normal in their combining power. When the total proteins were elevated an abnormal curve with rose bengal was always obtained, while, on the other hand, six of the forty-three pathologic fluids showed abnormal dye curves with normal protein content.

The cell count was elevated in forty-one of the forty-three cases but no quantitative relation existed between the number of cells and the results with other tests.

⁸ Mestrezat, W., quoted by Levinson (footnote 6)

⁹ Kafka. *Munchen med Wchnschr* 62 105, 1915

The colloidal gold reaction is a function of the proteins but its mechanism is not well understood. It is not given by normal spinal fluid and Weston¹⁰ isolated a globulin from pathologic fluids to which he attributes the discoloration of the colloidal gold. Further investigations on this problem were made by Felton,¹¹ Cruickshank,¹² Mellanby and Anwyl-Davies¹³ and Nixon and Naito.¹⁴ Pauli¹⁵ has shown that the color changes are due to a change in the valence of the gold from trivalency to pentavalency. The colloidal gold test differs fundamentally from the rose bengal test in that the former is not dependent on the total protein concentration, some proteins exert a buffer action on the gold sol while others discolor it and therefore maximum discoloration may occur only in high dilutions (syphilitic and meningitic curves). Hence, its chief value lies in differential diagnosis rather than as a quantitative method of analysis.

The gum mastic reaction appears to bear a more definite relation to protein content (review of literature in Cockrill¹⁶) although here, too, certain constituents of the spinal fluid may exert an action antagonistic to precipitation of the mastic. Keidel and Moore¹⁷ and Wassermann¹⁸ have shown that the "syphilitic zone" reaction is uncommon. Intermediate reactions (mastic 3 curves) were so frequent in normal persons as to render only the "paretic" mastic curve of reliance. In their hands the mastic test is somewhat more sensitive than the colloidal gold reaction. We have also found the mastic test very sensitive although its value in this respect is to some extent decreased by the wide variations that occur in normal fluids. In the present small group of cases studied, the rose bengal was superior to the gum mastic reaction as regards differential diagnostic value in general paralysis. In comparing these methods the statistics of Thompson¹⁹ and Wassermann¹⁸ on large groups of cases must be borne in mind. According to the latter observer, paretic curves occurred with a colloidal gold test in 86 per cent of general paralysis, 58 per cent of tabes and in 34 per cent of

10 Weston, P. G. *Am J Insan* **74**:431 (Jan) 1918

11 Felton, L. D. *New York M J* **105** 1170, 1917

12 Cruickshank, J. *Brit J Exper Path* **1** 71 (April) 1920

13 Mellanby, J., and Anwyl-Davies. *Brit J Exper Path* **4**:132, 1924

14 Nixon, C. E., and Naito, K. *Studies of Spinal Fluid and Blood of Syphilitic and Normal Persons with Special Reference to Immunity Reactions and Colloidal Gold Test on Original and Unfiltered Fluids and Serums*, *Arch Int Med* **30**:198 (Aug) 1922

15 Pauli, W. *Kolloid-Ztschr* **28**:49, 1921

16 Cockrill, J. R. *Arch Neurol & Psychiat* **14** 455 (Oct) 1925

17 Keidel, A., and Moore, J. E. *Arch Neurol & Psychiat* **6** 163 (Aug) 1921

18 Wassermann, H. *Comparative Results of Colloidal Gold and Colloidal Mastic Tests*, *Arch Int Med* **32**:401 (March) 1924

19 Thompson, L. J. *Arch Neurol & Psychiat* **5** 131 (Feb) 1921

cerebrospinal syphilis, with the mastic reaction the percentages were 91, 70 and 58, respectively

Refractometric Index — This has been recently employed as a clinical test on the spinal fluid by Molnar²⁰ and by Levinson and Serby²¹. Increase in the refractometric index is due mainly to augmentation of protein concentration. Levinson and Serby have shown that change occurs only when marked increases in protein content are present. Our observations are in accord with his and we do not feel that this method offers much promise as a diagnostic procedure.

COMMENT

With the multiplicity of tests now at hand for examination of the cerebrospinal fluid, one is hesitant to advocate a new procedure. However, as compared with other colloidal tests the rose bengal reaction promises to yield results of greater value than total protein determinations and to give quantitative results that are not brought out by the colloidal gold or mastic tests. Its place in the differential diagnosis of neurologic disorders remains to be established. From a technical point of view it is quite easy to carry out and results can be read at once, as the adsorption equilibrium of the reaction seems to be established immediately.

It is seen in the accompanying chart that the dilution values present some differences, as all the curves are not parallel. This is probably due to variations in the nature of the protein adsorbents. However, the 1:50 dilution reflects fairly well the height of the curve, and a rapid technic for bedside or routine use can be carried out on this dilution as follows: Into a flask marked to contain 58 cc., 1 cc. of spinal fluid is placed and made up to the mark with water. Rose bengal, 1 cc. of 0.1 per cent solution, should be added and mixed, then 1 cc. of 0.5 normal hydrochloric acid added. The solution is mixed by inverting the flask and some of the fluid poured into a test tube for comparison with the standard tubes described above.

Is it not possible that an increase in combining power represents one of the mechanisms on the part of nature to combat disease? This is suggested by the frequency with which an increase in adsorptive power occurred without a detectable increase in protein content, and by the fact that albumin, which has a high combining power, is always an important constituent of inflammatory exudates, even though the specific antibodies are associated mainly with globulins. Practically nothing is known of the surface phenomena that take place at the interfaces of the

20 Molnar, A. L. *Klin. Wchnschr.* 2:790 (April 23) 1923.

21 Levinson, A., and Serby, A. M. *Refractometric and Viscosimetric Indexes of Cerebrospinal Fluid*, *Arch. Int. Med.* 37:144 (Jan.) 1926.

colloidal (protein) micellae in the body fluids, and studies of colloidal behavior, especially of a quantitative nature, offers a wide scope of investigation as applied to body proteins in health and disease

SUMMARY

A colloidal reaction dependent on the adsorption of rose bengal has been applied as a quantitative test on the spinal fluid. The quantity of dye adsorbed is a function of both the concentration and the nature of the proteins present in the fluid.

The highest results were obtained in pyogenic and tuberculous meningitis. Twenty-four cases of untreated neurosyphilis gave abnormal values, and the results in general paralysis showed a tendency to be higher than those in tabes and cerebrospinal syphilis.

Seven of the forty-three pathologic fluids showed increased combining power for rose bengal, although no increase in the total proteins could be demonstrated.

PERISTALSIS IN A LOOP OF SMALL INTESTINE

A DIRECT STUDY †

LAURENCE E HINES, M D

AND

H C A MEAD, M D

CHICAGO

Knowledge of the movements of the small intestine has been obtained by various methods. The chief methods of study have been roentgenograms or fluoroscopy following an opaque meal, direct observation, after opening the abdomen of an animal submerged in a bath of physiologic sodium chloride solution at body temperature, observation of the changes in pressure produced in a thin walled rubber balloon inserted in the lumen of the intestine, and direct observation of excised intestine, kept alive in an oxygenated saline bath at body temperature.

This study is the direct observation of peristaltic movements in a loop of small intestine which was always present in an unusual congenital umbilical hernia of an old negro. The first observation at once impressed us that the case offered an unusual opportunity because the movements were so plainly seen.

The hernia was in the midline of the abdomen immediately above and continuous with the umbilicus. It contained intestine at all times and usually protruded about 4 cm. anterior to the skin level, although when the patient was on his back, the protrusion was less than when he was on his side or standing. The hernia was kidney shaped and measured 9 cm. across and 5 cm. up and down. The entrance to the hernial sac was an oval defect in the abdominal wall about 3 cm. in diameter. When pressure was applied to the hernia, the contents were reduced into the peritoneal cavity but the sac always filled quickly and assumed the original contour when pressure was released. The outer covering of the hernia was very thin skin and it was possible to grasp the intestinal loop between the fingers. When it was grasped in this way, firm pinching did not cause pain. The types of movement that were observed were a slow, almost imperceptible change in contour of the hernia, spasmodic or tonic contractions of the loop, and very rapid peristaltic waves, which usually extended along the long axis of the loop.

Direct observation of the slow movement was difficult and no information of any value was obtained.

* From the departments of Internal Medicine and Physiology of the Northwestern University Medical School.

* Aided by a grant from the Fenger Memorial Fund.

The spasmodic contractions occurred twice when the patient had a diarrhea and once when hunger was marked. They were associated with severe, cramp-like pain in the hernia.

The rapid peristaltic waves were energetic, rolling movements that traveled about 3 cm per second, measured roughly by drawing vertical lines on the skin, 1 cm apart. The waves varied from tiny, narrow streaks along the side or on the top to broad, deep ones which seemed to involve the entire free surface of the intestine. The waves usually started on the right side and extended along the long axis, either to traverse the field of observation or end in it. Frequently broad waves became narrower as they progressed and often terminated in a point. Waves of reverse peristalsis were frequently observed, especially during periods of active intestinal movement. They occasionally started distal to the loop of intestine and were observed first in the left side, but more frequently they started at the point and time of termination of a forward wave and passed back over the same course. Other observers have confirmed our observations of reverse peristalsis in this case.

Fluoroscopic observations with the aid of a barium meal were readily made because the intestinal loop was superficial and isolated. In one instance the barium meal passed from the esophagus to the loop in fifteen minutes and again in eighteen minutes. Several loops of small intestine were filled before the barium reached the hernia. Though the exact location of the loop cannot be stated definitely, it seems certain that the hernia contained small intestine, probably a loop of distal jejunum or proximal ileum. The barium first entered the right side in tiny amounts. By periodic addition of more barium, a large bolus-like mass soon collected. This moved rapidly backward and forward with a churning motion. Small portions were pinched from the bolus and passed distally while additional opaque material was added from above. Periods of quiet alternated quite regularly with such movement.

It seemed worth while to get detailed records of the duration and amplitude of periods of peristaltic activity, to show if possible their relation to such factors as hunger and food ingestion. Several preliminary observations and trials with recording devices led us to believe that mechanical methods would not record slight movements, especially since many of them occurred in small areas at the periphery of the hernia. We chose to record our observations manually on graph paper, in which ordinates represented twenty second intervals and abscissas five arbitrary degrees of the amplitude of peristaltic waves, expressed as one plus, two plus, etc. Preparatory to recording our observations, the patient was instructed to lie on the right side on a hard examining table with the hernia exposed before a bright light. The observer, with graph paper and a second watch at hand, was

seated at a small table immediately in front of the hernia. Close attention to the movements and timing was necessary to transfer to the paper dots or horizontal lines that expressed the approximate amplitude and duration of the movements. Two observers alternated for the longer periods. The method is to be criticized because it is not a precise one. The charts only represent graphic and quantitative expressions of the observer's impressions of the movement in the intestinal loop.

Sleeping

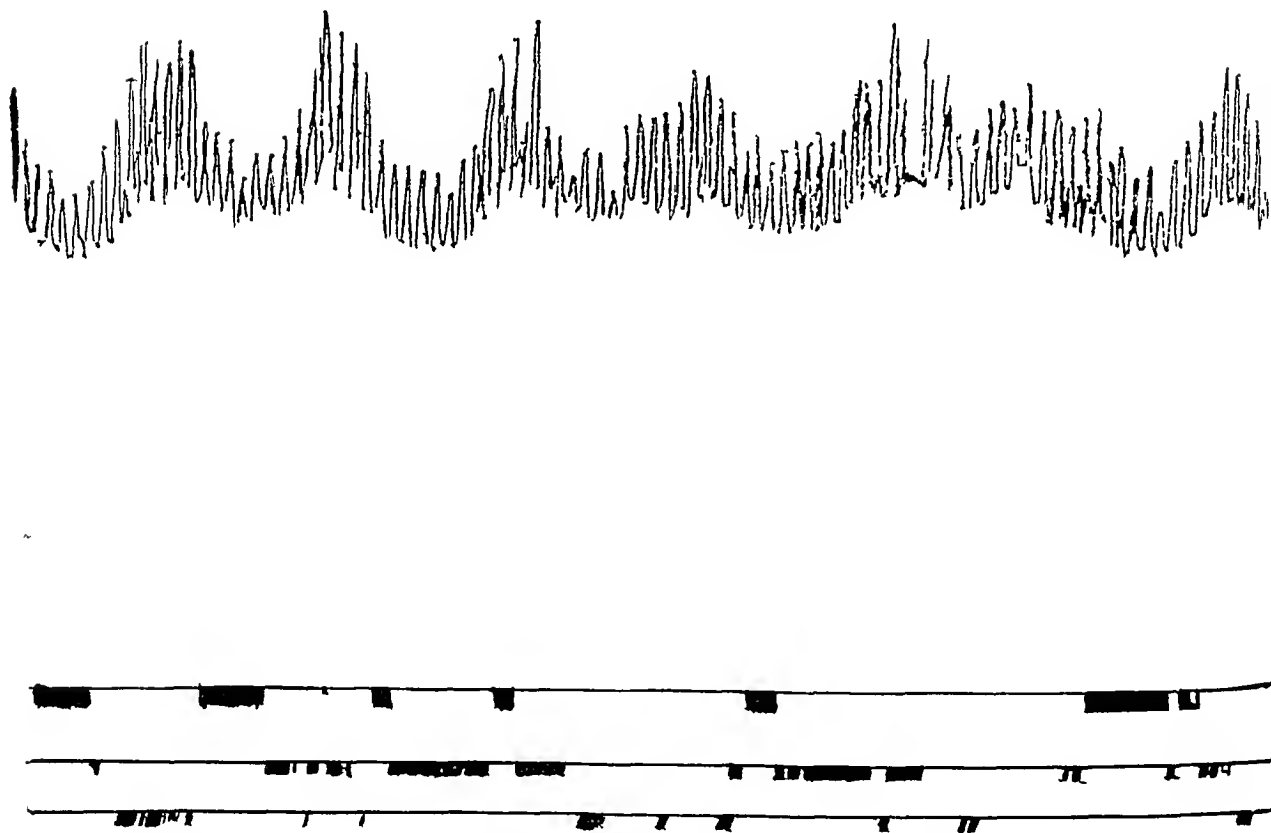


Fig 1—Tonus rhythm of stomach, moderate to marked movement in intestinal loop

Over fifty records were made by this method. It is impossible to interpret all the information because of the many uncontrollable factors, but detailed consideration of hunger is made in the accompanying table because of the number of times observed. As shown in the table, charts were made twenty-seven times when he was hungry (fasting from ten to thirty-six hours). In twenty-four instances, or 89 per cent, peristalsis

was marked or moderate while in the absence of hunger there was practically no movement, in eighteen of twenty-two instances (81 per cent)

He was observed four times when he had diarrhea and each time as shown in the table, there was marked or moderate peristalsis

Charts were made before and after the administration of buttermilk, milk, water, candy, fruits, bland diets, "ruffage" diets, sodium bicarbonate and epinephrine, but nothing definite was indicated

The patient fell asleep many times while charts were being made and there was no resultant change in the amount of movement

An attempt to compare peristalsis in the intestinal loop with simultaneous gastric contractions was made. An inflated intragastric balloon attached to a water manometer recorded gastric contractions on a slow drum. A triple signal magnet, placed immediately below the stylet which recorded gastric motility, was used by the observer to record three degrees of intestinal movement¹

Relation of Hunger and Diarrhea to Intestinal Movement

	Times Observed	Marked Intestinal Movement	Moderate Intestinal Movement	Slight or or No Movement
Hunger periods	27	20	4	3
Absence of hunger	22	4	1	18
Diarrhea	4	3	1	0

Three tracings showing only tonus rhythm in the stomach were associated with continuous activity (moderate and marked) in the intestinal loop. Before the balloon was inflated with air (from 50 to 150 cc), slight or no movement was present. Active movement started immediately after the balloon was inflated. Deflation of the balloon was not immediately followed by cessation of movement. Two tracings showed active hunger contractions and these also were associated with marked activity in the intestinal loop. These results indicate that active intestinal movements are initiated by intragastric distention. They do not point out any relation between gastric hunger contractions and intestinal movement.

NECROPSY FINDINGS

The patient died before our observations were completed and a necropsy was made about forty hours after death. The abdomen was opened by making a curved incision about 15 cm. to the right of the

¹ After this work was completed, Dr. A. C. Ivy demonstrated that major movements could be recorded with a plethysmograph that he had used for cardiometry. One with a window was being made preparatory to the taking of simultaneous tracings of the stomach and intestinal loop when the patient developed heart failure. He died before the procedure could be carried out.

hernia The hernial sac was empty and the coils of intestine were free in the peritoneal cavity Coils of proximal ileum were adjacent to the hernial opening, but there was no change of the outside of any loop to indicate that it had been in the hernial sac previously The great omentum was rudimentary The transverse colon lay high in the peritoneal cavity, several centimeters above the hernial opening The gastrocolic ligament was short The opening of the hernia was ovoid,

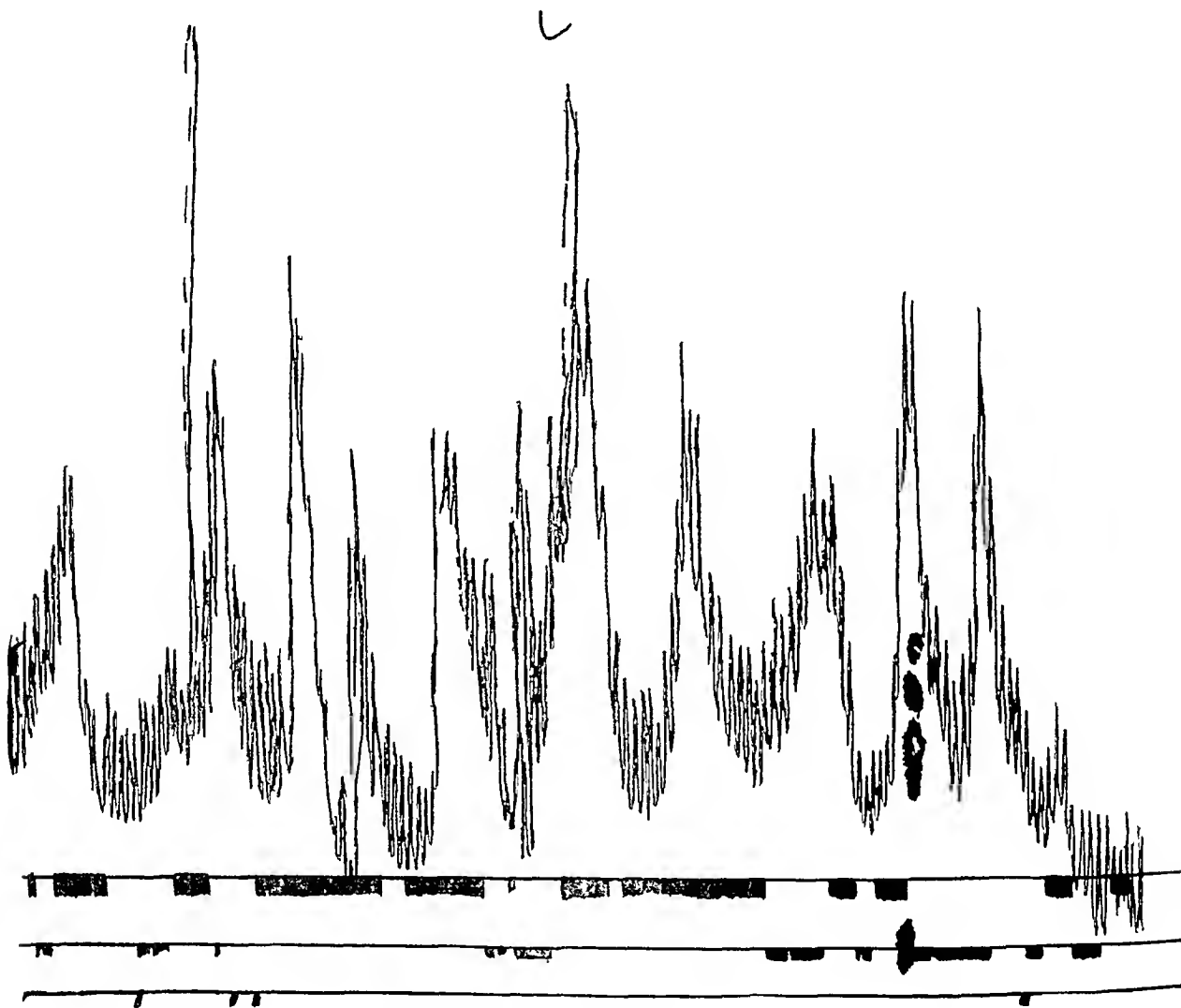


Fig 2—Gastric hunger contractions, marked movement in the intestinal loop

the long axis extending 3.2 cm vertically and the transverse diameter 1.8 cm The margins of the opening were cordlike and firm enough to prevent closure Smooth peritoneum covered the margins and extended into the hernial sac where it became very thin The wall of the sac was 0.3 cm thick, composed only of skin and peritoneum Inside, the sac was roomy, the long axis extending about 8 cm transversely

COMMENT

The results obtained from this investigation seem to throw some light on certain phases of intestinal movement. Activity in the small intestine is generally considered to consist of rhythmic segmentations, slowly advancing peristaltic waves and peristaltic rushes. The movements we have studied resemble the latter type. They varied from tiny rapid ripples to rolling movements propelled forward with marked energy and associated with rumbling of gas in the hernia. They often ceased abruptly after a period of violent activity to reappear later quite as abruptly. The fluoroscopic findings and the anatomic relations revealed at the necropsy showed that our observations were made on movements in the small intestine. Unfortunately, the precise loop in the hernia is not revealed, probably because the necropsy was made forty hours after death. At this time, there was no loop in the hernia despite the constant presence of one during life. The small ovoid opening of the sac, allowing the entrance of one loop only, the thin sac which made even slight movements easily visible and the absence of adhesions were factors that made a favorable subject for study. Furthermore, the normal physiology of the part was not interfered with by mechanical devices in the lumen of the bowel or by previous operative manipulations.

In 1916, Carlson² stated that the character of intestinal movement in hunger was not known, but he pointed out that there is some evidence which indicates that active contraction of the small intestine occurs in hunger, viz., the observations by Busch³ of active contraction of the small intestine during the hunger in a case of duodenal fistula, the occurrence of marked borborygmi during hunger periods noted first by Boldyreff⁴ and later by others, and Carlson's observations of evidences of contractions (expulsion of gas, fluid and debris) in duodenal fistula dogs during hunger. Recently more accurate methods for studying this question have been devised by Ivy and Vloedman⁵ and they have demonstrated, on man, contractions in the duodenum, synchronous with or immediately following gastric hunger contractions. They conclude that the duodenal motility is dependent on enteric reflex contractions within the stomach, since no related or synchronous contractions occurred in the duodenum of animals with Thiry's fistula or duodeno-

2 Carlson, A. J. *The Control of Hunger in Health and Disease*, University of Chicago Press, 1916.

3 Busch. *Arch f Pathol Anat* **14** 140, 1862.

4 Boldyreff. *Quart J Exper Physiol* **10** 175, 1916.

5 Ivy, A. C., and Vloedman, D. A. *The Small Intestine in Hunger*, *Am J Physiol* **72** 99 (March) 1925.

esophageal anastomoses Our observations confirm the presence during hunger of active movements in the small intestine distal to the duodenum and show further the type of movement present

The vigorous character of the movements was surmised by Carlson, who thought he could feel them through the abdominal wall The untimely death of the patient prevented us from determining the exact correlation of these movements with gastric hunger contractions

As vigorous intestinal movements were often observed during this study when there was no hunger pain, this may be taken as negative evidence that intestinal movement plays no part in the production of hunger pain Boiborygmus was usually present when intestinal movements were vigorous and gas could actually be felt in the loop of intestine This suggests that excessive distention of the wall of the intestine by collections of gas might be the stimulus of active movements, particularly since the waves extended not only analward, but were equally as vigorous in the opposite direction

It is a well known clinical observation that the pain in so-called colitis, or irritable bowel, follows food ingestion The production of active intestinal movements by intragastric distention suggests an explanation for this pain Furthermore, the commonplace occurrence of defecation, after breakfast, might be explained in the same way Such an explanation has been suggested previously in experiments by Ivy and McIlvaine⁶ who have shown that application of various irritating substances to the duodenum is often followed by defecation or vomiting or both

There is a rather general belief that retrograde movements occur normally only in the colon Of course, it has long been known that reverse peristalsis may occur in the small intestine under pathologic conditions such as the fecal vomiting in ileus, the vomiting of enemas and suppositories by hysterical women, and the occasional roentgen-ray observation of the flow of barium enemas into the duodenum Alvarez⁷ believes mild reverse peristalsis is common and explains on this basis many gastro-intestinal symptoms, such as vomiting, food regurgitation, pyrosis, nausea, and the coated tongue and foul breath associated with "biliousness" McLeod⁸ has noted in rabbits rhythmic to-and-fro shifting of masses of food in the small intestine Recently there have been reports of numerous fluoroscopic observations of duodenal reverse

6 Ivy, A. C., and McIlvaine, G. B. The Excitation of Gastric Secretion by Application of Substances to the Duodenal and Jejunal Mucosa, *Am. J. Physiol.* **67**: 124 (Dec.) 1923

7 Alvarez, W. C. The Syndrome of Mild Reverse Peristalsis, *J. A. M. A.* **69**: 2018 (Dec. 15) 1917

8 McLeod, J. J. *Physiology and Biochemistry in Modern Medicine*, St. Louis, 1922

peristalsis It has usually been attributed to duodenitis or other pathologic conditions, but Wheelon⁹ observed it in sixteen patients in which the duodenum was free from demonstrable pathologic changes It is probable that the general failure of roentgen-ray methods to appreciate reverse peristalsis in the small intestine is due to our inability to follow the opaque material after it leaves the duodenum Our observations indicate that reverse peristalsis is normally present when movements are active

SUMMARY

A man with congenital umbilical hernia containing a single loop of small intestine was used for the study of intestinal movements Active peristaltic waves were present in 89 per cent of hunger periods and in 19 per cent of nonhunger periods

Reverse peristalsis was observed consistently during periods of active movement It is probably normal in the small intestine

Active progressive and reverse waves were not usually associated with pain, but tonic spastic contractions were always accompanied by violent colicky pain The tonic contractions occurred twice during periods of diarrhea and once when hunger was the only complaint

Active intestinal movement was initiated by inflating an intragastric balloon

Intestinal movements were apparently neither inhibited nor accelerated during sleeping periods

⁹ Wheelon, Homer Symptoms Associated with Duodenal Retention and Reverse Motility, *J A M A* **86** 326 (Jan 30) 1926

AID IN THE DIAGNOSIS OF TYPHOID FEVER

A NEW LABORATORY METHOD *

C A MILLS, M D

AND

K V KITZMILLER, M D

CINCINNATI

In the course of our work on blood clotting, we came on a reaction which seems to differentiate typhoid fever from other infections. The reaction is given early in the disease, being therefore much more useful in diagnosis than is the Widal test. The difficulty of obtaining a positive blood culture, together with the delay in the development of a positive Widal reaction, gives added value to a reaction which is reliable and present throughout the active period of the disease. This reaction also sharply differentiates typhoid fever from another disease with which it is often confused, miliary tuberculosis.

We were engaged in measuring the antithrombic activity of the blood serum under a variety of conditions when we found that typhoid fever was differentiated from other fevers studied by us by a most intense antithrombin production throughout the fever period. An excess antithrombin production was found in cases of pulmonary tuberculosis, peptic ulcer and a few other conditions, most likely accounting at least in part for the frequency of hemorrhage in these conditions. But in none of these was the production equal to that in typhoid fever.

The method of measuring the antithrombin in the blood is as follows. Blood is withdrawn from an arm vein of the patient and quickly mixed with sufficient 50 per cent sodium citrate solution to give a final concentration of 0.5 per cent. This citrated blood is centrifugalized, the plasma pipetted off and 1 cc. of it heated to 60 C. for ten minutes in a water bath. This destroys the fibrinogen and prothrombin, but does not affect the antithrombin. Horse plasma, or other available plasma obtained from blood citrated to 0.5 per cent, is now caused to clot by recalcification and the serum squeezed quickly from the clot so that it may be used within ten minutes after the clotting. (About 0.2 cc. of 1 per cent calcium chloride solution is required to recalcify each cubic centimeter of citrated plasma and cause clotting.) To each cubic centimeter of the serum used is added 0.1 cc. of a 0.1 per cent emulsion of cephalin, and one minute allowed for complete activation of the prothrombin to thrombin by the cephalin. At the end of this minute the activated serum is pipetted into tubes (2 cc. to each tube) and

* From the Laboratory for Experimental Medicine, Department of Internal Medicine, University of Cincinnati College of Medicine

to one tube is added 1 cc of 0.5 per cent sodium chloride solution, to another the 1 cc of heated human plasma. Three or four bloods may be tested in one series, using the one control, when one has become familiar with the method. Two, five, ten, twenty and thirty minutes after preparing the foregoing mixtures of serum and saline solution or heated plasma, 0.3 cc is taken from each and added to 0.5 cc of citrated horse (or other) plasma (in a water bath at 40 C). The time taken by each sample to clot the horse plasma is considered to represent its thrombic activity. As time passes the thrombin disappears from the serum-saline tube at a certain rate, while its disappearance from the serum heated plasma tube is at about twice this rate in typhoid fever. Samples from the latter tube, therefore, clot citrated plasma more and more slowly, the thrombic activity diminishing more rapidly

TABLE 1—*Results of Experiments*

Tube 1	
0.5 cc citrated plasma + 0.3 cc of mixture in tube 1 (2 minutes old)	clots in 10 seconds
0.5 cc citrated plasma + 0.3 cc of mixture in tube 1 (5 minutes old)	clots in 10 seconds
0.5 cc citrated plasma + 0.3 cc of mixture in tube 1 (10 minutes old)	clots in 15 seconds
0.5 cc citrated plasma + 0.3 cc of mixture in tube 1 (20 minutes old)	clots in 40 seconds
0.5 cc citrated plasma + 0.3 cc of mixture in tube 1 (30 minutes old)	clots in 65 seconds
Similar Tests Simultaneously Carried Out with Tube 2	
0.5 cc citrated plasma + 0.3 cc of mixture (2 minutes old)	gave clotting in 9 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (5 minutes old)	gave clotting in 10 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (10 minutes old)	gave clotting in 18 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (20 minutes old)	gave clotting in 40 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (30 minutes old)	gave clotting in 67 seconds
Tube 3	
0.5 cc citrated plasma + 0.3 cc of mixture (2 minutes old)	clotting occurred in 10 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (5 minutes old)	clotting occurred in 16 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (10 minutes old)	clotting occurred in 29 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (20 minutes old)	clotting occurred in 80 seconds
0.5 cc citrated plasma + 0.3 cc of mixture (30 minutes old)	clotting occurred in 120 seconds

than in the control. Blood from a normal person will give readings about the same as the control tube.

Let us illustrate an actual test, with readings. Blood is obtained from a normal person and from a typhoid fever patient, citrated, centrifugalized, and 1 cc of each plasma heated to 60 C for ten minutes. While this is heating, 15 cc of citrated horse plasma is clotted by the addition of 3 cc of 1 per cent calcium chloride solution. The serum is quickly squeezed from the clot in the hand, and to 6 cc of this serum is added 0.6 cc of 0.1 per cent cephalin emulsion. This procedure is timed so that the activated serum is ready at the time the plasmas have been at 60 C for the ten minute period.

Tube 1 is prepared containing 2 cc of activated serum and 1 cc of 0.5 per cent sodium chloride solution.

Tube 2 is prepared containing 2 cc of serum and 1 cc of heated normal plasma.

Tube 3 contains 2 cc of serum and the 1 cc of heated plasma from the typhoid patient

These three tubes are left at room temperature. Tubes containing 0.5 cc of citrated horse (or other) plasma are placed in a water bath at 40 C. When the three tubes containing the foregoing mixtures have stood for two minutes, 0.3 cc is taken from each and added to the tubes of citrated plasma in the water bath and the clotting time noted. This is repeated at the end of five minutes after making the serum mixtures, after ten, twenty and thirty minutes. The results are given in table 1

TABLE 2—*Antithrombic Content of Typhoid Plasma*

Patient	Date	Temperature	Laboratory Data		Antithrombin Curve
			Widal	Blood Culture	
1	10/ 7/25	Maintained	1 160	Positive	1 25, 2 5, 2 86, 2 1, 2 3
	10/10/25	Falling			12, 0 85, 0 84, 0 7, 0 72
	10/26/25	Normal			10, 10, 12, 10, 11
2	10/ 7/25	98 to 101	1 160	Negative	1 25, 4 5, 4 3, 3 5, 2 3
	10/10/25	98 to 101			20, 1 3, 2 2, 1 4, 1 3
	10/26/25	Normal			10, 10, 12, 10, 13
3	10/24/25	Falling	Negative	Positive	1 25, 1 9, 1 4, 1 3, 1 2
	10/27/25		1 160	Negative	
	11/ 2/25				
4	10/29/25	Maintained	1 160	Positive	10, 2 1, 20, 1 4, 1 2
	11/ 2/25	Slowly falling			20, 10, 20, 1 3, 1 4
	11/12/25	Slowly falling			40, 3 3, 4 4, 30, 30
	11/30/25	Normal			0 8, 0 7, 0 9, 0 9, 1 1
5	11/ 2/25	99 to 101	1 20	Positive	10, 12, 10, 10, 12
	11/ 5/25	High, maintained			10, 10, 11, 12, 15
	11/ 9/25	High, maintained			20, 30, 20, 2 3, 30
6	11/20/25	102 to 103.5	1 100	Negative	10, 19, 17, 1 4, 1 4
	11/24/25	102 to 103			13, 12, 12, 0 9, 0 9
	12/ 3/25	98.6 to 101			10, 17, 12, 11, 11
7	11/28/25	101 to 104	Negative	Negative	10, 11, 12, 1 3, 1 2
	12/ 1/25	98.6 to 100		Negative	1 4, 11, 1 4, 1 4, 2 7
	12/ 4/25			1 160	
8	12/ 8/25	102 to 104.5	1 80	Negative	1 3, 1 2, 2 4, 1 4, 1 1
9	12/ 8/25	Falling	1 80	Positive	1 6, 1 2, 1 4, 1 1, 1 1
10	12/18/25	Falling, 102 to 103	1 160	Positive	1 3, 1 4, 1 8, 2 1, 2 1
	1/ 4/26	Normal			0 6, 0 8, 1 9, 1 9, 1 7
	1/14/26	Normal			0 6, 0 5, 0 8, 10, 11
11	1/21/26	101 to 104	1 160	Positive	1 4, 1 8, 2 1, 1 4, 1 3
	1/25/26	101 to 105			10, 12, 10, 16, 16
	2/ 1/26	97.5 to 101			0 9, 10, 12, 2 7, 20
12	1/25/26	High maintained	1 20	Positive	10, 0 8, 0 7, 0 8, 1 2
	2/ 1/26	Falling			11, 1 4, 20, 3 4, 2 9
	2/16/26	Normal			0 6, 0 7, 1 2, 1 1, 1 1
13	2/16/26	High, maintained			10, 16, 20, 20, 1 9

If we represent the clotting time of the control tube at each time of testing as unity and calculate the clotting time with the other tubes as decimals of this, we get the following for normal plasma 0.9-1.0-1.2-1.0-1.02, and for the typhoid plasma 1.0-1.6-1.95-2.0-1.85. This method of expression means that the curve of antithrombic activity in both the normal and typhoid plasma reaches its maximum after ten or twenty minutes standing with the serum, and that the antithrombin in the typhoid plasma destroys the thrombin of the activated serum at

twice the rate of the control. Variations with normal plasma may be found ranging between 0.8 and 1.3, but we have found all typhoid cases to have plasma giving a curve the peak of which usually exceeds 2. We have chosen this method of expression of the curve of antithrombic activity in the different plasmas as most nearly depicting what we desire to show. It is, of course, quite similar in manner of expression to the gold curve for spinal fluid.

Table 2 gives the results of antithrombic tests on the plasma from typhoid cases (diagnosis verified by Widal or blood culture) and on a number of other plasmas in normal persons and patients suffering from various diseases.

In table 2, are listed all the typhoid fever cases that have been available for study in the Cincinnati General Hospital since Oct. 1, 1925. Some of these patients had been sick for several weeks and had a falling temperature on admission. We have indicated in one column of the table the temperature behavior, since that has considerable significance in interpreting our results. Of the thirteen cases presented, all but three gave an antithrombic curve exceeding 2 at some point. Of the three exceptions, patient 3 (maximum 1.9) and patient 9 (maximum 1.6) had falling temperatures when the blood samples were obtained, while case 6 (maximum 1.9) was a very mild case.

In one case, case 7, the first blood taken for a Widal test was reported negative (Nov. 28) and the diagnosis of typhoid fever was seriously doubted. Our test gave a maximum of 2.7 in the antithrombic curve December 1, so the Widal test was repeated December 4, and found positive in dilution of 1:160.

The antithrombic curve diminishes as the fever abates in most cases, and in most of the blood samples taken after the temperature has been normal for some time the antithrombic content has been less than normal.

In one case, case 5, the first two samples of plasma showed no increased antithrombic content, while the third one showed a great increase, with the peak at 3. Another case, case 12, showed a normal reaction at the first test, and later gave the typical increase in antithrombin.

Of the several hundred plasmas tested by us since last October, a few have given antithrombic curves within the range of those listed in table 2. We have grouped these tests in table 3 along with tests on plasmas of patients suffering with miliary or pulmonary tuberculosis, or both. Of these cases listed in this table only two presented any possibility of confusion with typhoid fever at the time the blood was drawn. Of these two, patient 14 was a boy with a high maintained fever for two days before typical lobar pneumonia findings developed. There was a high polymorphonuclear leukocytosis from the onset, however, so the

chance for confusion with typhoid fever was slight. The other, patient 15, had a fever for only two days. Her leukocyte count was 4,900 with 55 per cent lymphocytes. She appeared to be suffering from an influenzal infection. The Widal test in both cases was negative.

We have had a number of cases that have somewhat simulated typhoid fever clinically for a few days, and have given high antithrombic curves, only to develop jaundice later and appear as frank cholecystitis or catarrhal hepatitis. These we have not listed in our tables of results because we early discovered that any increase of bile salts in the blood would destroy thrombin just as does the blood antithrombin. We, there-

TABLE 3—*Antithrombic Content of Nontyphoid Plasma*

Patient	Date	Antithrombic Curve	Clinical Diagnosis and Remarks
14	12/10/25	14, 20, 20, 18, 18	Lobar pneumonia developed the next day
15	2/16/26	11, 15, 19, 18, 16	Toxic erythema, leukocyte count, 4,900, 55 per cent lymphocytes
16	2/19/26	17, 17, 17, 14, 18	Furunculosis, pericarditis, malnutrition, no fever
17	2/ 8/26	14, 12, 16, 25, 23	Aortic insufficiency aortitis, cardiac hypertrophy and dilatation, pulmonary congestion, no fever
18	2/ 1/26	15, 19, 15, 13, 24	Vascular syphilis, no fever
19	1/31/26	16, 14, 14, 16, 15	Tuberculous adenitis, no fever
20	2/ 3/26	14, 16, 18, 20, 20	Syphilis aortitis and dilatation, aortic regurgitation, cardiac hypertrophy and dilatation, cardiac decompensation, chronic passive congestion of viscera
21	2/22/26	25, 27, 36, 60, 37	Cardiorenal, syphilitic, no fever
22	1/21/26	12, 18, 22, 18, 31	Normal
23	10/27/25	10, 13, 11, 10, 10	Normal
24	10/28/26	10, 10, 13, 12, 11	Miliary tuberculosis, pulmonary tuberculosis, advanced
25	10/30/25	10, 09, 08, 06, 06	Miliary tuberculosis
26	1/25/26	07, 08, 06, 09, 12	Miliary tuberculosis, tuberculous meningitis
27	2/16/26	07, 06, 11, 10, 09	Miliary tuberculosis, far advanced pulmonary tuberculosis
28	2/16/26	07, 07, 12, 11, 09	Far advanced pulmonary tuberculosis, syphilitic meningitis
29	11/23/25	06, 07, 12, 11, 11	Pulmonary tuberculosis
30	11/19/25	15, 16, 14, 15, 15	Pulmonary tuberculosis
31	11/19/25	10, 11, 13, 11, 11	Pulmonary tuberculosis
32	11/19/25	10, 10, 07, 08, 09	Pulmonary tuberculosis
33	10/ 8/25	10, 10, 12, 13, 10	Pulmonary tuberculosis, hemorrhage one month before
34	10/ 8/25	10, 13, 15, 12, 11	Pulmonary tuberculosis
35	10/ 8/25	12, 16, 12, 10	Pulmonary tuberculosis, frequent hemorrhage
36	10/ 8/25	13, 17, 14, 10	Pulmonary tuberculosis

fore, do not perform the test on the blood of jaundiced patients. Occasionally a patient with a high antithrombin curve will delay the appearance of jaundice for a few days, but practically always the van den Bergh reaction for bile pigment will be positive as early as the antithrombic increase is evident in those cases that later do develop jaundice.

The next six cases in table 3, cases 16, 17, 18, 19, 20 and 21, gave antithrombic readings of the range found in typhoid fever, but none of these patients had fever, so no difficulty in differential diagnosis arose. Four of these were cases of vascular syphilis, with more or less decompensation, one was tuberculous adenitis, and the other, case 16, had a chronic infection of undetermined type—all were distinctly chronic

infections We have often found an antithrombin increase in various states of chronic infection, but not often of the degree found in these six cases The upper limit in such infections as pulmonary tuberculosis, streptococcic endocarditis, fungulosis, etc., is usually around 1.6 or less

The next four cases listed in table 3 are cases of miliary tuberculosis, two of them also with far advanced pulmonary tuberculosis and one with meningitis, while the fifth had far advanced pulmonary tuberculosis and a brief meningitis, which was thought to be syphilis The antithrombin curves here are highly significant, since miliary tuberculosis is one of the diseases most often confused with typhoid fever, and in which the differential diagnosis is most difficult A negative Widal and blood culture do not rule out typhoid fever, and with the clinical pictures of the two conditions so similar, one is often kept in considerable doubt It is, therefore, very important to note that the antithrombin curve is entirely dissimilar in the two conditions, the miliary tuberculosis having constantly less than normal values, thus differentiating this condition sharply from typhoid fever with its large excess of antithrombin

The last seven cases listed were chosen from among the inmates of the Branch Hospital for Tuberculosis, to demonstrate the antithrombin curves associated with various stages of pulmonary tuberculosis Active pulmonary tuberculosis, uncomplicated by other infections, always exhibits an increase in the blood antithrombin As the infection subsides, the antithrombin also returns to normal We believe the reason for the continuance of many pulmonary hemorrhages in tuberculosis lies mainly in this condition of the blood, with the immediate cause of the onset of bleeding being the erosion of a vessel by the destructive process

COMMENT

In our measurement of the antithrombin production in typhoid fever we have demonstrated a reaction constantly associated with this disease and but rarely found in other conditions that might be confused clinically with typhoid fever That it should be found in certain afebrile conditions such as vascular syphilis with decompensation, pericarditis and tuberculous adenitis does not detract from its value in the diagnosis of typhoid fever The only two confusing cases found were those of patient 15 with a two day fever and patient 14, who promptly developed lobar pneumonia We have constantly found pneumonia itself to be just the opposite of typhoid in its antithrombin production, so no difficulty of differentiation presents

It is fortunate that two diseases with which typhoid fever are most often confused, early pneumonia and miliary tuberculosis, should present antithrombic curves so widely divergent from those of typhoid fever

It is as yet beyond our ability to explain the significance of this great antithrombin production in typhoid fever. We believe it to be the first step in the immunity reaction, the back swing of the pendulum that must precede the swing to positive immunity. This phase of the matter is receiving our attention at present, and offers a most interesting lead into the study of the immune mechanism.

One point in our work seems evident, that we here have the explanation for the bleeding tendency so constantly associated with typhoid fever. The physical erosion by the ulcers provides the opportunity for the onset of intestinal bleeding, it is true, but the reason for the dangerous character of such bleeding, and for the epistaxis, lies in the altered condition of the blood as here demonstrated. In another article we will discuss this blood change in its relation to a variety of conditions exhibiting a hemorrhagic tendency.

It is hoped that this report will stimulate others to try the test in available typhoid fever cases so that its true worth and significance may be ascertained. Our supply of clinical material is so limited that years of waiting would be necessary for collecting the needed laboratory data from the cases we have in this place alone.

SUMMARY OF RESULTS

1 The results of tests on thirteen typhoid patients demonstrate a high antithrombin production during the febrile period, with practically twice the normal antithrombin content in every case.

2 All but two of the nontyphoid cases that showed this high antithrombin production were afebrile cases of a distinctly chronic character, so that no confusion in diagnosis was possible. One of the two exceptions was a boy with high fever, negative physical findings and high leukocytosis, who two days later developed typical lobar pneumonia. The leukocytosis here would have practically ruled out typhoid fever. The other exception was a young girl whose fever lasted only two days, and on whom no diagnosis was made before discharge from the hospital.

3 Miliary tuberculosis, so often confused with typhoid fever, is entirely different in its antithrombin curve. Here, instead of a great excess of antithrombin, there is actually less than normal. This gives a differential diagnostic point that promises to be of great value.

4 A logical basis is established for explaining the hemorrhagic tendency in typhoid fever.

Book Reviews

FACTS ON THE HEART By RICHARD C CABOT, M D, Professor of Medicine and Social Ethics, Harvard University Pp 781, 163 illustrations Cloth, \$7.50 Philadelphia W B Saunders Company, 1926

This book represents an approach to the study of heart disease from a rather new angle. A careful study and statistical review of 1,906 cardiac cases out of a total of 4,000 necropsies at the Massachusetts General Hospital between 1896 and 1919 is presented. Thus we learn that nearly half of all subjects examined at necropsy at this hospital during this period suffered from some cardiovascular lesion, also, after making certain allowances, to quote, "a cardiovascular lesion is an important factor in 38 per cent of all deaths." As Cabot states, no similar book or study exists as far as he knows. It is unfortunate, however, that it is not possible to obtain necropsies in all of a large series of fatal cases in which cardiovascular disease was either diagnosed or suspected. Such a study might alter, to a certain extent at least, some of the conclusions, some support for this contention is to be found by a study of table 5, in which the incidence of the various forms of heart disease is given for each 1,000 necropsies performed.

The work is divided into twelve chapters and a final summary of the book. The first chapter is given over to the incidence, frequency and type of cardiac disease and the remaining chapters are devoted to case reports, protocols and comment. These reports do not represent the work of one person but are the combined observation and study of a large group of the medical staff, Cabot has compiled and edited the statistics and various facts to be gleaned from them and has drawn certain conclusions, some of which are rather startling both in that they seem too dogmatic and at times radical, particularly is this true, in regard to mitral regurgitation and myocarditis. The words "must," "always" and "never" should be deleted from medical literature.

If the book is read with due consideration of the shortcomings incident to statistical compilations and with a knowledge of contemporary writings on this subject, it will prove to be interesting and valuable, particularly in that it is so well written and by a clinician of such large experience.

RHEUMATIC HEART DISEASE By CARY F COOMBS, M D, F R C P (LONDON), with an introduction by F J POYNTON, M D, F R C P (LONDON) Pp 376, 51 illustrations Price, \$4.50 New York William Wood & Co, 1924

The opening sentence in the preface is rather surprising. The author states that it "is a remarkable fact that so familiar a feature of everyday practice as rheumatic heart disease has not hitherto been made the subject of a monograph." This treatise is not a compilation or a critical review of the work of others, but represents a long personal study and survey of the disease as it has occurred in the experience of the author. There is, however, a short bibliography at the end of each chapter and an excellent index is appended. Dr Poynton suggested this problem to the author in 1903 and an intensive study and survey were made in Bristol during the next twenty years. The work was further stimulated by the interest of Sir Clifford Allbutt and greatly aided by several grants from the Medical Research Council. The book is well illustrated and is divided into eleven chapters which discuss in detail the etiology, histology, physiology, pathology, symptomatology, diagnosis, course, prognosis, treatment and prevention. Of greatest practical value to the student and clinician are the chapters on physical signs, and on the course and prognosis, the latter is, indeed, a very important and valuable contribution. The author is cognizant

of the organized campaign which is being waged in America against heart disease and commends it highly, particularly the matter of placing cardiac cripples in suitable and remunerative employment

FIBRILACION Y FLUTTER AURICULAR By DR MANUEL VELA GONZALEZ Seville
Tipografia de Gerones

This monograph of fifty-seven pages is the address by the author on the occasion of his induction into the Royal Academy of Medicine of Seville. It is profusely illustrated with polygraph tracings and electrocardiograms, representing the results of the study of twenty-two cases of auricular fibrillation and flutter.

Most of the paper is taken up with a discussion of the action of quinidine in these cases. His review of the literature shows that of 379 patients treated with this drug, the normal rhythm was restored in 190, almost exactly half. On the basis of the circus movement theory of Mines and Garry, which has been elaborated by Lewis and Mackenzie, he has attempted to explain the action of the drug. While digitalization can produce an improvement in the rhythm by bringing on heart block, quinidine action on the auricle itself, by the prolongation of the refractory period, may bring it about that the entire cycle is filled by the contraction wave and the refractory period, and thus regularize the contractions of the auricle.

It must not be forgotten that some persons are very susceptible to this drug and cannot tolerate it. For that reason medication must be initiated with small doses and discontinued if any untoward symptoms occur. Finally restoration of the normal rhythm does not necessarily restore compensation. In the decompensated cases digitalis may be required to increase the force of the heart beat, and as the two drugs are mutually antagonistic, the tonic effect of the digitalis may be needed more than the quinidine effect. Alternation of dosage may then be indicated.

CHEMICAL CHANGES IN THE BLOOD DURING FASTING IN THE HUMAN SUBJECT¹

WILLIAM G LENNOX[†]

WITH THE ASSISTANCE OF

MARIE O'CONNOR

AND

MARGARET BELLINGER

BOSTON

Although there have been extensive studies of the metabolism of fasting men and animals, as revealed by examinations of the urine and the expired air, comparatively little has been written concerning alterations in the concentration of various chemical constituents of the blood. During the last three years we have conducted thirty fasting periods in which we have measured various blood constituents. The most striking alteration of the blood was found to be a greatly increased concentration of uric acid. This observation, together with a study of the factors affecting uric acid retention during fasting, has been published.¹ This article deals with observations on the concentration in the blood of nonprotein, urea and amino-acid nitrogen, sugar, cholesterol, fibrin, inorganic phosphorus, total calcium and plasma bicarbonate. Observations concerning chlorides will be presented elsewhere.

MATERIAL AND METHODS

Of the thirty fasting periods, twenty-four were of persons who were fasted as a therapeutic measure for the relief of convulsions. The remaining six periods were of two healthy persons who acted as normal controls. Of the twenty-four subjects studied, two-thirds were male and one-third female. Ages ranged from 13 to 42 years. A series of

¹ From the laboratory of the department of neuropathology, Harvard Medical School, the medical service of the Massachusetts General Hospital and the Thorne-dike Memorial Laboratory of the Boston City Hospital. This research was made possible through a grant by the Committee on Epilepsy, New York City. This paper is no. 50 in a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

[†] Fellow in Medicine of the National Research Council during the greater portion of this research.

1. Lennox, W. G. Increase of Uric Acid in Blood During Prolonged Starvation, *J. A. M. A.* 82: 602 (Feb. 23) 1924, *J. Biol. Chem.* 66: 521 (Dec.) 1925.

observations, published² and unpublished, has shown that the blood of persons subject to convulsions contains normal amounts of sugar, of bicarbonate and of the nonprotein nitrogenous constituents. We believe that in the main the alterations in blood chemistry, which we will describe, have nothing to do with the tendency toward convulsions which these patients exhibit, but are normal physiologic adjustments to fasting. Possible exceptions to this rule will be pointed out later.

TABLE 1—Measurements of Nonprotein Nitrogen of Blood During Fasting

		Subjects										
		1	1	2	3	4	5	6	7	8	9	10
		(first)	(second)	Mg per 100 Cc of Whole Blood								
Food	1				35.2					38.7		
	2				37.7		31.6			37.5		
	3				36.8		42.0		33.4	39.3		
	4	39.4			34.8	41.0	35.9		34.3	35.3	32.8	30.3
Fast	1	30.9	44.0			38.0	39.2			43.5		26.7
	2		33.8			44.0	30.4	31.6	34.7	42.2	30.6	40.3
	3	35.5		41.8	52.2	40.0	35.2	33.4	45.4		41.1	38.7
	4			34.2				32.1	48.2		35.3	34.3
	5	31.5	45.2	33.0	39.7		29.8	34.3	48.0	44.4	38.7	33.8
	6			40.5			37.3	32.5	41.3	42.2	31.8	35.7
	7	36.8	39.2	40.5	32.1	42.2	37.3	34.0	41.3	40.0	35.7	30.2
	8				34.9	37.0	37.7	37.0	40.8	35.4	28.9	26.7
	9					39.2	33.5	36.2	41.3	39.5	36.4	33.3
	10	36.3	33.3		37.5	37.7	29.7	35.7	36.4	40.0	29.7	30.1
	11		30.5	37.4		28.2	25.6	31.9	34.9	46.2	34.7	26.8
	12	35.1		35.1	32.4			31.6	32.4	44.4	33.5	24.4
	13					37.0		37.5	40.0	30.0	38.9	24.6
	14	28.5	37.5	28.5		31.9		32.5	41.4	33.3		
	15			40.5		26.6	24.0			28.6		
	16		50.0									
	17	27.8*										
	18		54.5									
	20		38.0									
	21		27.9									
	Food	1	29.2	30.0	40.4	37.9	27.8	25.5	33.4	42.8	37.5	41.1
2		35.4	31.2	30.0	24.5	31.9	26.1	33.7		38.0		21.8
3		35.2		37.7	28.5	30.6	28.6	33.9		38.7	31.6	
4		31.1		30.6	20.6	23.4	24.0	35.3		32.4	28.6	
5				30.0	21.6	31.3	26.0	25.2				
6				28.2	27.2	27.9	27.5			29.3		
7				28.8	32.6	38.7						
8				32.4	27.8	33.0						
9				28.0	30.4	33.7						
10				31.6	26.1	33.9						24.6
11				30.0	31.4	32.7						
12				29.2	33.3	40.8						
13					29.2	42.0						
14					31.6	38.7						

* In this and subsequent tables, the last measurement recorded during fast marks the end of the fasting period.

Fasting periods varied in length from three to twenty-one days. The usual length was fourteen days. Except in a few instances, water intake was unlimited. In some periods, as will be noted in the tables, certain substances were given during fasting in order to study the effect on uric acid retention. All patients except one, patient 4, were confined to the ward during fasting. The healthy subject (subject 11) continued

his usual laboratory work Unless otherwise noted, fast was broken by means of mixed, purine free, low protein diet Before and after the period of fast, blood was drawn in the morning before breakfast Approximately 20 cc was taken daily It is not probable that withdrawal of this small amount influenced the concentration of the constituents studied There was no significant decrease in the percentage of hemoglobin Observations by Dr H S Forbes at the end of a fifteen day fast of patient 4 showed no increase in the number of reticulated red cells

The following methods of analysis were used blood nonprotein and urea nitrogen, Folin-Wu,³ amino-acid nitrogen, Folin,⁴ sugar, Folin-Wu,⁵ calcium, Kramer and Tisdall,⁶ inorganic phosphate, Bell and Doisy,⁷ cholesterol, Bloor,⁸ plasma bicarbonate, Van Slyke,⁹ fibrin, Foster and Whipple¹⁰

NONPROTEIN NITROGEN

Table 1 gives the measurements of nonprotein nitrogen during and subsequent to eleven fasting periods Inspection of the table shows for most of the periods, variable values from day to day, with a tendency toward higher measurements during the fasting periods Only a few of these measurements, however, were abnormally high Increases, when they occurred, were transient Thus, during the second fast of patient 1, nonprotein nitrogen per hundred cubic centimeters of blood was 54 mg on the eighteenth day, and 28 mg on the twenty-first day These fluctuations are presumably explained by uneven catabolism of body protein The fact that the level of circulating nitrogen may vary so greatly from day to day suggests that the amount of nitrogen excreted daily may not exactly measure (as it has been assumed to do) the amount of protein being catabolized in the body In other words, small variations in nitrogen excretion may be merely the reflection of variations in the level of circulating nitrogen in blood and tissues

In the period of refeeding subsequent to fasting there was in almost all cases a definite decrease in the level of nonprotein nitrogen in the blood The question arises whether such decrease was due to increased elimination of nitrogen or to increased synthesis of nitrogen by the tissues In a person weighing 70 Kg a decrease of nonprotein nitrogen

3 Folin, O, and Wu, H J Biol Chem **38** 81 (May) 1919

4 Folin, O J Biol Chem **51** 377 (April) 1922

5 Folin, O, and Wu, H J Biol Chem **41** 367 (March) 1920

6 Kramer, B, and Tisdall, F F J Biol Chem **47** 475 (Aug) 1921

7 Bell, R D, and Doisy, E A J Biol Chem **44** 55 (Oct) 1920

8 Bloor, W R, Pelham, K F, and Allen, D M J Biol Chem **52**:191 (May) 1922

9 Van Slyke, D D J Biol Chem **30**:347 (June) 1917

10 Foster, D P, and Whipple, G H Am J Physiol **58** 365 (Jan) 1922

of 20 mg per hundred cubic centimeters of blood, if it were excreted in the urine, would increase the total urinary nitrogen by approximately 1.3 Gm. In several instances we found that coincidentally with the resumption of food, and the reduction in nonprotein nitrogen in the blood, less nitrogen was excreted than was ingested. It would seem probable, therefore, that the nonprotein nitrogen which leaves the blood after fasting is not excreted but is used in building body protein.

TABLE 2—Measurements of Urea and Amino-Acid Nitrogen of Blood During Fasting

		Subjects					
		2		3		1 (first)	
		Mg per 100 Cc of Whole Blood					
Diet	Day	Urea Nitrogen	Amino Acid Nitrogen	Urea Nitrogen	Amino Acid Nitrogen	Urea Nitrogen	Amino Acid Nitrogen
Food	1			16.6	6.5		
	2			15.3	6.6		
	3			14.6	7.1		
	4			14.3	6.2		
Fast	1						
	2						
	3	16.4	6.6	21.7	6.1	17.6	6.3
	4	13.6	6.5				
	5	13.0	6.1		6.4	13.0	6.3
	6	17.6	6.0				
	7	17.5	5.3		6.7	15.8	5.5
	10			15.8	6.4	15.0	6.8
	11		7.2				
	12		6.2	13.3	6.1	14.2	6.5
	13						
	14	15.0	5.8			11.5	6.5
	17					9.5	6.2
Food	1	16.4	5.8	13.1	5.3	8.8	
	2	15.3	6.5	8.8	6.5	10.8	5.3
	3	15.8		9.8	5.8	11.5	6.5
	4	12.0	7.3	8.3	6.1		5.2
	5	13.9	5.9	11.2	5.6		
	6	13.0	6.1	12.5	5.9		
	7	15.0	5.1	15.0	5.4		
	8	15.0	5.4	11.7	6.1		
	9	11.2	5.3		6.3		
	10	14.3	5.2		6.2		
	11	14.4	5.5		7.2		
	12	11.7	6.7	15.4	6.8		

UREA AND AMINO-ACID NITROGEN

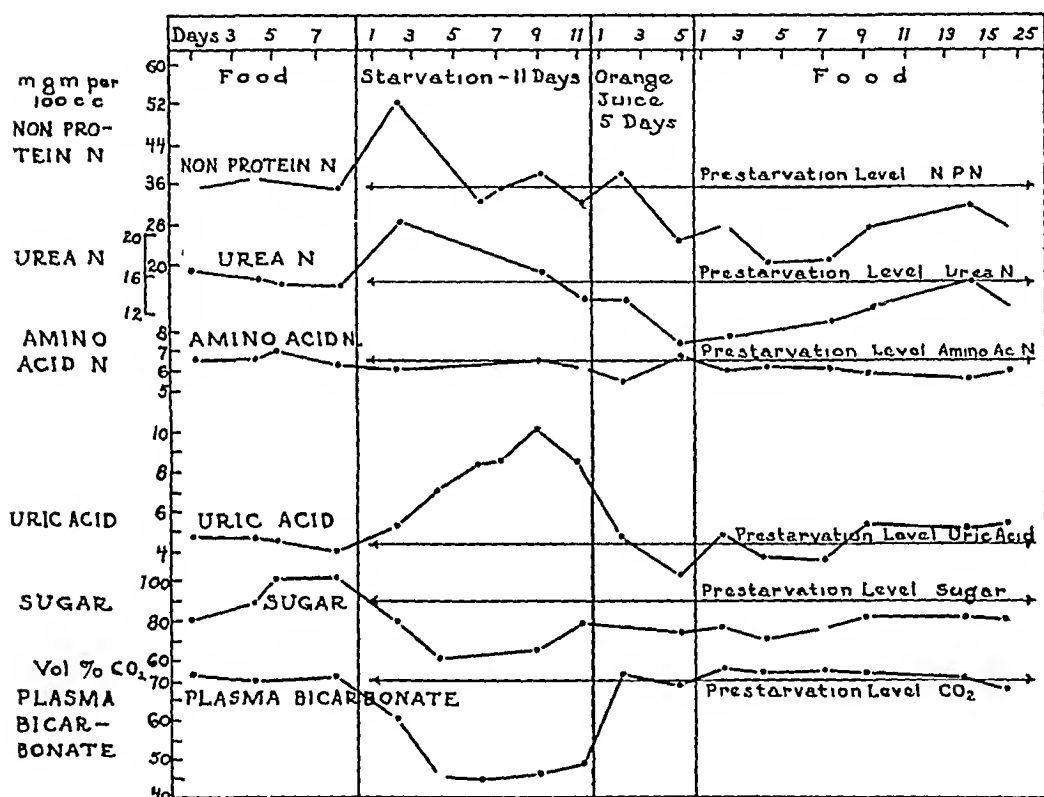
Table 2 shows that the concentration of urea nitrogen during fasting behaved in the same manner as nonprotein nitrogen. In contrast, the amino-acid nitrogen remained remarkably constant, both throughout fasting and the subsequent period of refeeding. From measurements of the amino-acid nitrogen of the blood, we would never suspect that profound metabolic disturbances of the body were in progress. The constancy of the level of amino-acids in the blood during fasting is in agreement with observations of their normal concentrations in a variety of diseases¹¹ and under various experimental conditions¹².

11 Greene, C. H., Sandiford, K., and Ross, H. J. Biol. Chem. **58** 643 (Jan.) 1924.

12 Okada, S. and Hayashi, T. J. Biol. Chem. **51** 121 (March) 1922.

The accompanying chart presents a comparison of various chemical constituents of the blood during the fast of patient 2. It will be noted that nonprotein and urea nitrogen concentrations ran parallel, that amino-acid nitrogen remained constant, and that uric acid increased without reference to the other nonprotein nitrogenous constituents.

Observations detailed in tables 1 and 2 were made at intervals of from one to several days. Table 3 gives measurements at short intervals (from four to twelve hours) during three fasting experiments of healthy subject 11. In the first fast the greatest variation in concentra-



Comparison of the concentration of nonprotein, urea and amino-acid nitrogen, uric acid, sugar and plasma bicarbonate in patient 3 during and subsequent to fasting.

tion was 13 mg for nonprotein nitrogen and only 0.6 mg for amino-acid nitrogen. During the second and fourth fasts undertaken by this subject, variation in nonprotein nitrogen was not so great, a fact observed by Morgulis and Edwards¹³ during a second fast of a dog.

Table 4 presents a comparison of all the nonprotein nitrogenous constituents on the twenty-first day of fasting of subject 1 in comparison with two days after the resumption of a low protein, purine free diet. In the two samples total nonprotein nitrogen was the same. At

the end of the fast uric acid and rest nitrogen were higher, and urea, amino-acid and creatinine lower than two days later

There are few published observations that are strictly comparable to our own Morgulis and Edwards¹³ measured the nonprotein nitrogenous constituents in the blood of seven dogs during and subsequent

TABLE 3—*Measurements of Nonprotein Nitrogen of Blood at Short Intervals During Three Fasts of Healthy Subject 11*

Blood Sample	Amino-Acid Nitrogen Mg per 100 Cc of Whole Blood	Nonprotein Nitrogen, Mg per 100 Cc of Whole Blood		
		First Fast	Second Fast	Fourth Fast
1		28.6	37.4	34.3
2	5.5	31.6	36.8	30.3
3	5.0	28.3	35.3	30.4
4	5.1	30.3	33.9	33.4
5	5.1	30.0	34.3	31.6
6	5.6	31.9	34.3	34.3
7	5.3	26.8	34.7	28.6
8	5.5	35.3	35.0	42.3†
9	5.1	39.5	36.4	33.2
10	5.3	40.3	35.3	38.5
11	5.6	41.2	35.3	46.2‡
12	5.0	40.0	37.4	32.2
13	5.8	43.5	34.5	36.8
14			33.4*	34.3
15			34.9	34.9
16			33.2	
17			33.7	
18			33.4	
19			30.8	
20			33.4	
21			32.1†	
22			35.8	
23			31.6	
24			30.4	

First fast, duration fifty four hours Blood taken at four hour intervals throughout Last sample taken two and one-half hours after food

Second fast, duration four days Blood taken at intervals of from two to twelve hours

* Seventy five grams of soda bicarbonate taken during subsequent twenty-four hours

† Beginning of mixed diet

Fourth fast duration seven days Blood taken three to five times a day

‡ Blood taken several hours after ingestion of 25 Gm of asparagine and 85 Gm of protein, respectively

TABLE 4—*Constituents of Blood on Twenty-first Day of Fast and Two Days After Resumption of Food (Second Fast of Subject 1)*

Diet	Mg per 100 Cc of Whole Blood							Sugar
	Non protein Nitrogen	Urea Nitrogen	Amino- Acid Nitrogen	Uric Acid Nitrogen	Creat- inine Nitrogen	Creatine Nitrogen	Rest Nitrogen	
Last (21st) day of fasting	27.9	12.9	5.9	3.3	0.71	0.9	4.2	62
After two days of food*	27.1	14.3	8.1	1.1	0.46	1.2	1.9	95

* Blood taken eighteen hours after food

to fasting Their dogs were fasted till they lost approximately 40 per cent of their body weight, whereas the majority of our subjects lost only about from 10 to 15 per cent of their initial weight During this stage of 10 per cent loss, Morgulis and Edwards, in order to avoid changes due to anemia, drew blood from their dogs but once Haden

and Orr¹⁴ made daily measurements during an eleven day fast of a single dog. Hoeffel and Moriarty¹⁵ have published observations on three fasting children and Harding and associates¹⁶ on a group of patients fed on a low caloric high fat diet. Though our material and methods differ somewhat from those used by these writers, our results are in substantial agreement with theirs.

SUGAR

In the eight fasts tabulated in table 5, the level of sugar in the blood declined during the first week of fasting, after which it rose to nearly its prefasting level. The curves for blood sugar and plasma bicarbonate

TABLE 5—Measurements of Sugar of Blood During Fasting

Diet	Day	Subjects									
		11	2	4	9		12		13	14*	20
		Normal	Blood,	Blood,	Blood,	Plasma,	Blood,	Plasma,	Plasma,	Plasma,	Blood,
		Blood,	Mg	Mg	Mg	Mg	Mg	Mg	Mg	Mg	Mg
Mg per 100 Cc											
Food	1						92	87		78	74
	2	78	92	99	98		95	87	93	77	84
Fast	1	102		85	98	88	103	84	88		80
	2			68	92	83	77	68	68	78	
	3		85	69	77	69	59	54	65	52	
	4	68	88	70	80	70	59	56	59	49	45
	5		77	69	77	64	55	53	68	51	44
	6		77	83	70	65	61	55	69	54	
	7	78	68	72	73	67	60	54	74	59	53
	8			73	72	66	59	61	76		53
	9	80		82	81	79	69	67	72		55
	10			73	75	72	73	65	72		53
	11		66	68	75	71	70	68	64		58
	12	81	67	75	78	78	83	80	69		
	13			96	75	72	86	82	75		
	14		63	74					78		
	15	77		84							
	16			69							
Food	1	91	93	79	86	95	90	84	88		58†
	2	103	83	84			89	84	91		59
	3		80	99	87	83	82	78	85		59
	4			102	97	88	73	66	92		56
	5			110			83	76			54
	6			99			70				59
	7			100			81				

* Sugar measurements for this period made by the method of Benedict.²⁸

† High fat diet

ran a roughly parallel course. During fasting, concentration of sugar in the blood could be increased by injection of epinephrine. Concentration of glucose in plasma was constantly lower than in whole blood. In the latter, glucose did not fall below 55 mg per hundred cubic centimeters, except in the case of the youngest member of the group, a girl of 13 years (subject 20), in whom the blood sugar fell to 44 mg.

14 Haden, R. L., and Orr, T. G. *J. Exper. Med.* **37**:365 (March) 1923.

15 Hoeffel, G., and Moriarty, M. *Am. J. Dis. Child.* **28**:16 (July) 1924.

16 Harding, V. J., Allin, K. D., Eagles, B. A., and Van Wyck, H. B. *J. Biol. Chem.* **63**:37 (Feb.) 1925.

Evidently the condition in children differs from that in adults. During five fasting periods in children, Shaw and Moriarty¹⁷ encountered a very low level of blood sugar. The average minimum amount in their children was 46 mg, whereas in our adults it was 65 mg.

Weeks and associates¹⁸ made weekly measurements of blood sugar in seventy-three epileptic patients fasted for three weeks. These patients and the dogs of Morgulis and Edwards¹³ showed, after an initial drop, increasing concentrations of sugar in the blood as the fasts progressed.

CHOLESTEROL

Table 6 gives the results of measurements of cholesterol during the fast of three patients. (The observations in this table are not controlled by data from healthy subjects.) The results are conflicting. The first

TABLE 6—Measurements of Cholesterol During Fasting

Diet	Day	Mg per 100 Cc of Plasma		
		Subject 15	Subject 8	Subject 16 (Serum)
Food	1		190	
Fast	1	91		
	2	93		
	4		143	159
	5			101
	6	118		
	7		140	
	8	132		
	9	154		
	10	156	152	
	11	174		
				•
Food	1			190
	4		186	
	7			286

patient 15 had a very low concentration of cholesterol in the blood at the beginning of the fast. The amount increased steadily during eleven days of fast. The patient died shortly after so that postfasting readings were not secured. With two other patients cholesterol was much lower during fasting than before or after. These conflicting observations are similar to results obtained with animals.

Bloor¹⁹ found that blood fat increased during the first four or five days of fasting in three dogs and remained constant in three. One of the latter, when stuffed with fat and starved again, showed increase of fat in the blood. Greene and Summers²⁰ found that blood fat increased

17 Shaw, E. B., and Moriarty, M. Hypoglycemia and Acidosis in Fasting Children with Idiopathic Epilepsy, *Am J Dis Child* **28** 553 (Nov.) 1924.

18 Weeks, D. F., Renner, D. S., Allen, F. M., and Wishart, M. B. *J Metabolic Res* **3** 201 (Feb.) 1923.

19 Bloor, W. R. *J Biol Chem* **19** 1, 1914.

20 Greene, C. W., and Summers, W. S. *Am J Physiol* **40** 146 (March) 1916.

in fasting puppies and remained constant in fasting dogs. With regard to cholesterol, Terroine²¹ reported a progressive decrease during the prolonged fasting of dogs. Rothschild,²² on the contrary, found an increase in four rabbits fasted from two to nine days.

TOTAL CALCIUM AND INORGANIC PHOSPHORUS

Gamble, Ross and Tisdall²³ found no change in plasma calcium at the end of four days of fasting in a child. Bigwood²⁴ found increase but his measurements were calculated values for ionized calcium. We have seen no observations concerning the behavior of blood phosphorus

TABLE 7—Measurements of Inorganic Phosphorus and Calcium During Fasting

Diet	Day	Phosphorus, Mg per 100 Cc of Plasma					Calcium, Mg per 100 Cc of Plasma				
		Sub- ject 11 (Normal)	Sub- ject 15	Sub- ject 8	Sub- ject 17 (Serum)	Sub- ject 16 (Serum)	Sub- ject 11 (Normal)	Sub- ject 15	Sub- ject 8	Sub- ject 17 (Serum)	Sub- ject 16 (Serum)
Food	1			3.53					11.6		
	2			3.13	3.3				10.3		
Fast	1	5.0			3.25		12.3				
	2	3.5	2.8				15.0	12.6		12.6	
	3	3.1	2.6				14.6	11.5		11.4	
	4	2.4	2.4	2.50		2.91	12.5	11.1	10.6		
	5				2.78						12.0
	6										11.9
	7			2.50					9.1		
	8				2.25	2.86				12.3	
	9			4.17 2.86					13.87 17.1		
	10		2.6 2.9	4.17				10.0 11.4	13.8		
	11		3.0	2.23		2.50		12.0	15.5		11.3
	12		2.5		3.33			11.8		11.6	
	13								9.9		
	14		2.0					12.9			
Food	1		2.4			3.33		13.9			9.3
	2										
	3		2.6					12.1			
	4		3.0	2.50	2.30				10.5		
	5			2.50	2.63					11.1	
	6									14.4	
	7			3.60		2.50					10.2

in fasting. The four epileptic subjects whose calcium and phosphorus we measured during fasting (table 7) showed no significant variations from their normal levels, except that one patient who was given 30 Gm of calcium chloride by mouth showed subsequent increase in the calcium of his plasma. The normal control who fasted four days showed increase in blood calcium and coincident decrease in phosphorus during a four day fast. The period was unsatisfactory, however, because, for other purposes, fasting was preceded by the ingestion of 79 grains (5 Gm.) of thyroid extract.

21 Terroine, E. F. *J. de physiol. et de path. gen.* **16** 386, 1914.

22 Rothschild, M. A. *Beitr. z. path. anat.* **60** 227, 1915.

23 Gamble, J. L., Ross, G. S., and Tisdall, F. F. *J. Biol. Chem.* **57** 633. (Oct.) 1923.

24 Bigwood, E. J. *Compt. rend. Soc. de biol.* **90** 98 (Jan. 25) 1924.

TABLE 8—Measurements of Blood Fibrin During Fasting

Diet	Day	Mg per 100 Cc					
		Plasma			Whole Blood		
		Subject 4	Subject 12	Subject 13	Subject 4	Subject 12	Subject 13
Food	1			418			246
	2			416			239
Fast	1	373			184		
	2	336	300		166	169	
	4	301			180		
	5	305	345		137	192	
	6	385			168		
	8		351			206	
	10	355		364	150		224
	11		323			189	
	13	297			159		
	14		323			192	
	15	272			147		
Food	2	314			152		
	4	291		345	154		208
	7	303			164		
	10	359	332		170	207	
	11	374			191		
	21	382			213		

TABLE 9—Measurements of Plasma Bicarbonate During Fasting

Diet	Day	Subjects										
		11	5	1	18	7	19	8	4	9	13	14
		Per Cent by Volume Carbon Dioxide (second)										
Food	1				68 0		61 2	68 5			66 8	
	2	70 0			65 3	66 3	58 2	70 4			65 0	75 3
Fast	1	69 7	60 3	60 7	63 8	64 2	60 2	69 8	56 6	61 0	64 5	73 8
	2	62 2			59 0	57 4	62 3	69 0	53 7	49 3	54 1	71 4
	3	48 6	59 3		55 2	50 1	53 7	65 5	43 9		44 7	51 8
	4	40 5	54 0	47 0			56 4	61 4	47 6	55 3	37 9	49 8
	5	33 2	40 5	52 5	55 9	55 7	47 0	60 7	48 5	54 2	36 5	49 1
	6	36 4	43 2		60 2	55 3		59 7		52 4	39 4§	46 1
	7	45 1	37 2	49 0	58 5	53 4	50 0	57 0	46 5	54 8	43 7	47 7
	8	44 7	40 4		60 7	55 6	51 2	61 1	48 0	48 1	44 6	
	9	52 1	44 5		59 5	55 1	55 5*	44 4†	45 9	50 3	45 6	
	10	49 6				59 2	53 0	51 7	44 9	57 7	41 1	
	11	54 0	48 3		59 8	56 5	51 3	61 0		57 5	44 6	
	12	54 0		53 2	57 2	63 2		87 0‡	44 5	63 3	47 2	
	13	52 3	49 5		59 3	55 5		77 8	48 0	63 0	45 5	
	14	51 0	49 4		63 0	52 5	60 8	74 0	76 6		40 2	
	15	49 3	45 7		59 0		67 3	65 3	66 4			
	17			53 3	57 4		60 3	63 5				
	19			58 2								
	21			55 0								
Food	1	66 0	59 5		68 3		64 7			76 5	49 6	
	2	72 5		68 5	69 0		69 5	71 4			63 9	
	3	73 2	71 0		73 0			74 5		77 0	63 6	
	4	72 5	68 5		68 5		65 0	69 5		66 0	64 2	
	5	74 4	63 5		68 8		67 2	68 6			65 4	
	6	77 8					66 0				71 6	
	7	75 0	65 0				65 3					
	8	68 2										
	9	66 3										
	10	67 5										

* Fifty four grains (3.5 Gm.) thyroid extract taken during subsequent five days

† Thirty five grains of calcium chloride taken during following forty-eight hours

‡ An alkaline mixture taken during following forty-eight hours

§ Severe vomiting, given 50 Gm. of glucose.

FIBRIN

We have seen no observations concerning the behavior of blood fibrin during fasting. In the three fasts of patients detailed in table 8 it will be seen that there was considerable fluctuation in values from day to day. Measurements during fasting tended to be lower in two cases and slightly higher in one.

PLASMA BICARBONATE

That reduction in the bicarbonate of the plasma attends the ketosis of fasting is well known. This has been demonstrated in rabbits by Asada²⁵ and in human subjects by Koehler,²⁶ Gamble, Ross and Tisdale,²³ Shaw and Moriarty,¹⁷ Bigwood²⁷ and others.²⁸ Table 9

TABLE 10—*Titratable Acidity of Urine and Excretion of Ammonia During Fourteen Days' Fast of Healthy Subject 11*

Diet	Day	Titratable Acidity			Ammonia			pH	
		Night	Day	24 Hours	Night	Day	24 Hours	Night	Day
Fast	1	230			0.34	0.13	0.47	5.3	5.9
	2	280	271	551	0.26	0.33	0.66	5.5	5.4
	3	211	369	610	0.60	0.84	1.44	5.4	5.3
	4	420	396	816	1.32	1.23	2.55	5.3	5.4
	5	385	345	730	1.25	1.38	2.63	5.4	5.7
	6	257	216	473	1.20	1.36	2.56	5.9	6.0
	7	167	157	324	1.28	1.24	2.52	6.0	6.0
	8		182		1.17	1.31	2.48	5.9	5.8
	9	122	153	275	0.80	1.27	2.06	6.0	6.3
	10	152	167	319	1.14	1.21	2.35	6.3	6.1
	11	187	169	356	1.34	1.06	2.40	6.0	6.1
	12	154	148	302	1.06	1.27	2.33	6.1	6.2
	13	113	133	246	0.85	0.92	1.77	6.2	6.1
	14	141	136	277	0.99	0.97	1.96	6.1	6.1
Fat	1	131	112	243	0.84	0.94	1.78	6.0	6.4
Low fat	1	74	52	126	0.40	0.14	0.55	6.6	6.5
Protein	2	41	40	81	0.15	0.16	0.31	6.4	6.2
	3	43			0.15			6.2	5.9

presents daily measurements of plasma bicarbonate (carbon dioxide combining power of the plasma) in normal subject 11 and seven patients. Inspection of the table shows the following:

In every case there was reduction of plasma bicarbonate but the amount varied in different subjects. The greatest reduction occurred from the third to the seventh days of fast. After the first week the acidosis gradually diminished, and plasma bicarbonate tended to approach the prefasting values. Following the ingestion of food, there was an increase of bicarbonate to above the prefasting level, a mild degree of alkalosis.

Two measurements of pH of the blood were made during two fasts of normal subject 11. On the fifth day of the first fast when plasma

25 Asada, H. *Am J Physiol* **50** 1 (Oct) 1919

26 Koehler, A. E. *Acid-Base Equilibrium*. Clinical Studies in Alkalosis, *Arch Int Med* **31** 590 (April) 1923

27 Bigwood, E. J. *Ann de med* **15** 119 (Feb) 1924

28 Benedict, S. R. *J Biol Chem* **64** 207 (May) 1925

bicarbonate was 33 per cent by volume, p_H of the blood was 7.2 (measured by D₁ Bock by means of carbon dioxide dissociation curve) On the third day of a fourth fast, the p_H of the blood was 7.37 (measured by Dr Koehler by gas chain method) In this subject, therefore, the depletion of bicarbonate of the blood resulted in an uncompensated acidosis It will be noticed that the patients showed a smaller reduction of bicarbonate than the normal subject Whether this is due to the fact that they were less active during the fast or to some inherent tendency against development of acidosis in epilepsy is not yet clear

ACID EXCRETION

As a corollary to the observations concerning the plasma bicarbonate of normal subject 11, table 10 presents data concerning acid and ammonia excretion It will be observed that titratable acidity was greatest during

TABLE 11—*Concentration of Various Constituents During a Short Fast Without Water of Normal Subject 11*

	Day	Water Intake, Ce	Mg per 100 Ce of Plasma				Bicarbonate per Cent by Volume Carbon Dioxide	Hemoglobin (Sahli)
			Nonprotein Nitrogen	Uric Acid	Sugar	Fibrin		
Prefasting	1	3,550		3.2	90		73.8	
	2	1,800		3.4	95	358	68.6	81.2
Fast	1	None		3.4	90		70.7	
			22	3.4				
			23	4.8	76		62.3	
	2	None	30	4.7	68		54.8	
			33	5.6				
			26	6.2	71	374	53.8	91.5
	3	None	33	6.2	62		52.0	
			35	7.1			54.9	104
			29	7.7	68	429	52.5	104
	4	2,500	31	8.6	70		48.0	
			30	9.3			47.2	101
Postfasting*	1	1,800	21	8.9	75		50.2	
			18	8.3			57.7	
	2	2,400	26	4.2	99	354	57.7	
	3		23	3.4	104		68.5	

* A three day interval between this and preceding observation

the period when depletion of bicarbonate was greatest With the increase in titratable acidity, there was increased excretion of ammonia, so that after the first few days the p_H of the urine remained practically normal

FASTING WITHOUT WATER

In a six day fast of healthy subject 11, no water was taken during the first seventy-five hours (table 11) During this period, plasma bicarbonate did not fall nor uric acid rise so fast as in previous fasts in which water was drunk This was presumably due to the unusually rapid destruction of body protein, as evidenced by increased basal metabolism rapid loss of body weight, and marked fluctuation in the concen-

triation of nonprotein nitrogen in the plasma (comparison should be made with table 3) The question of protein metabolism in fasting will be discussed in more detail elsewhere The increase of fibrin during the period without water could be accounted for largely by anhydemia, for there was coincident increase in hemoglobin from 81 to 104 per cent

SUMMARY

Observations of chemical changes in the blood made during and subsequent to thirty fasting periods of epileptic and normal subjects showed the following

During fast nonprotein and urea nitrogen varied considerably from day to day, with a tendency toward increased concentration, amino-acid nitrogen remained remarkably constant and uric acid rose independently of other constituents examined In the period of refeeding, nonprotein and urea nitrogen and uric acid fell to subnormal levels

Sugar fell to a low level during the first week, rising again as the fast progressed Concentration in plasma was constantly lower than in whole blood

Inorganic phosphorus and calcium remained constant, and cholesterol and fibrin showed both increase and decrease (three patients)

Plasma bicarbonate was greatly reduced, coincident with increase in total acid excretion

In a three day fast without water, there was evidence of unusual increase in protein metabolism

THE OUTPUT OF THE HEART PER BEAT IN HYPERTHYROIDISM *

I M RABINOWITCH

AND

ELEANOR V BAZIN

MONTREAL, CANADA

In a previous article¹ the measurement of the output of the heart per beat, by direct determination of the oxygen contents of arterial and venous blood, was shown to be a practical clinical procedure. Marked and consistent differences were noted between the values obtained in normal persons and in those with heart failure. The results in normal subjects agreed very closely with those obtained by other methods employed by physiologists and regarded as reliable. Briefly the test consists of the simultaneous determination of (a) the oxygen contents of arterial and venous bloods, (b) the oxygen requirement of the tissue per minute, and (c) the pulse rate. From these are calculated in order (a) the oxygen consumption, that is, the difference between the arterial and venous oxygen contents, (b) the total output of blood per minute from the heart, and (c) the output per beat. Thus, $T = \frac{100 \times R}{P(A - V)}$, in which

T = output per beat (cubic centimeters)

R = oxygen requirement (cubic centimeters per minute)

A = arterial oxygen content (cubic centimeters per hundred cubic centimeters)

V = venous oxygen content (cubic centimeters per hundred cubic centimeters)

P = pulse rate

The most probable objection which may be made to this procedure is to the assumption that values of the oxygen content of venous blood taken from arm veins are the same as in the blood in the right heart. It is generally recognized that variations in the oxygen content of blood from an arm vein may be caused by conditions other than the volume output of the heart. Of special note are temperature of the environment and muscular activity. This objection may be met with in at least two ways. It was shown (1) that in normal persons *under the constant set of conditions described* the variations in the oxygen unsaturation of venous blood in this region were remarkably constant and small. Numerous analyses made since have given the same results. The wide

* From the Department of Metabolism, Montreal General Hospital

1 Rabinowitch, I M. The Output of the Heart Per Beat in Heart Disease, Arch Int Med 36 239 (Aug) 1925

fluctuations recorded by different authors have been met with only occasionally. The comparative data are shown in table 1. These observations alone suggest the reliability of this procedure. The important fact, however, is that the results obtained in normal persons agree with those obtained by other methods of determining circulation rates and regarded as reliable. This has recently received confirmation as the following observations demonstrate.

Field, Bock, Gildea and Lathrop² recently determined circulation rates in normal resting subjects. Their method involved simultaneous determinations of alveolar and venous carbon dioxide tensions. From some of their data it was possible to compare the results of both methods. These authors recorded in each case the oxygen capacity of the blood, the oxygen saturation of venous blood and the rate of carbon dioxide

TABLE 1—*Variations in Oxygen Unsaturation of Venous Bloods*

	Venous Oxygen Unsaturation	
	Cc	Average
10 normal persons (authors' cases) published	35 to 55	4.2
42 normal persons (authors' cases) unpublished	30 to 52	4.4
55 persons with anemia (Lundsgaard)	25 to 55	
40 determinations on 4 subjects with compensated heart lesions (Lundsgaard)	15 to 56	
15 normal persons (Harrop)	26 to 88	
12 normal persons (Lundsgaard)	25 to 90	
12 patients with compensated heart lesions (Lundsgaard)	25 to 80	

elimination. From the data representing the oxygen capacity and the oxygen saturation of the venous bloods, one may calculate their oxygen contents. If the arterial bloods are assumed to be 95.4 per cent saturated with oxygen, and the average respiratory quotient in the postabsorptive state is accepted as 0.82, it is then possible to obtain, respectively, values for the oxygen contents of the arterial bloods and oxygen consumptions by the tissues per minute. From these data one may then calculate the circulation rates as above and compare them with those actually found. Thus

Subject F. W. L. (Field, Bock, Gildea and Lathrop)

Oxygen capacity = 20.0

arterial oxygen content = $0.954 \times 20.0 = 19.1$ cc

Oxygen saturation of venous blood = 77 per cent

Venous oxygen content = $20.0 \times 0.77 = 15.4$

Oxygen consumption = $(19.1 - 15.4) = 3.7$

Carbon dioxide elimination per minute = 20.4 cc

Respiratory quotient = $0.82 = \frac{20.4}{x}$ where x = oxygen consumption per minute by tissues

2. Field, H., Bock, A. V., Gildea, E. F., and Lathrop, F. L. The Rate of the Circulation of the Blood in Normal Resting Individuals, *J. Clin. Investigation* **1**: 65, 1924.

Oxygen consumption per minute = 248.7 cc

Circulation rate per minute = $\frac{248.7 \times 100}{37} = 672$ liters

The value actually found by Field, Bock, Gildea and Lathrop in this case was 703 liters

All the rates recorded by Field, Bock, Gildea and Lathrop were recalculated as above. The combined data are recorded in table 2. In order are recorded (a) the oxygen capacity, (b) calculated arterial oxygen contents, (c) percentage venous oxygen saturation, (d) calculated venous oxygen contents, (e) oxygen consumption, (f) carbon dioxide elimination rates, (g) calculated oxygen requirements, (h) calculated circulation rates, and (i) actual circulation rates (liters per minute). The results are striking as the following average values show.

Actual circulation rate (Bock et al) = 797 liters per minute

TABLE 2—Actual (Bock et Al) and Calculated (Authors' Method) Circulation Rates

Subject	Oxygen Capacity	Calculated Arterial Oxygen Content (s) × 0.954	Percentage Saturation Venous Blood	Calculated Venous Oxygen Content (a) × (c)	Oxygen Consumption (b) — (d)	Carbon Dioxide Elimination, Cc per Minute	Calculated Oxygen Requirement, Cc per Minute 0.82 × (f)	Calculated Circulation Rate, Liters per Minute	Actual Circulation Rate, Liters per Minute
F W L	200	19.1	77.0	15.4	3.7	204.0	248.7	6.72	7.03
F W L	199	19.0	76.6	15.2	3.8	204.0	248.7	6.54	6.69
F T H	182	17.4	74.0	13.5	3.9	139.3	170.0	4.36	4.50
O M J	215	20.5	83.0	17.8	2.7	171.5	209.1	7.74	7.80
O M J	203	19.4	83.2	16.9	2.5	155.0	189.0	7.16	7.64
J M F	180	17.2	77.2	13.9	3.3	201.7	246.0	7.48	7.47
A V B	200	19.1	70.8	14.2	4.9	190.3	232.1	4.74	4.76
A V B	216	20.6	75.0	16.2	4.4	174.2	212.4	4.80	4.84
H F	201	19.2	83.4	17.2	2.0	200.0	243.9	12.20	12.90
H F	208	19.8	83.6	17.4	2.4	208.0	253.6	10.60	10.40
H F	196	18.7	84.8	16.7	2.0	200.0	243.9	12.20	11.70
H F	221	21.1	82.6	18.3	2.8	193.8	236.3	8.40	8.40
H F	210	20.0	84.3	17.7	2.3	213.0	259.7	11.30	11.20
S L W	226	21.6	74.0	16.7	4.4	214.0	261.0	6.04	5.30
H P S	217	20.7	82.1	17.8	2.9	212.0	258.5	8.91	9.00
Average								7.94	7.97

Calculated circulation rate (authors') = 794 liters per minute

Subsequently observations to be discussed presently further demonstrated the reliability of this procedure.

During a study³ made in testing the theory of ammonia formation by the kidneys, it was found necessary to obtain data relative to circulation rates. The subjects were carefully selected for this purpose. They were all severe diabetes patients with marked acidosis. That they were ideal subjects to test the clinical value of this method of determining circulation rates will be observed from the following considerations.

A bright red color of the skin is frequently associated with the severe acidosis of diabetes. This color is usually accompanied by a

3 Rabinowitch, I. M., and Bazin, Eleanor V. Ammonia Formation by the Kidneys, to be published.

TABLE 3—Circulation Rates of Severe Diabetic Patients with Acidosis and Increased Basal Metabolic Rates

No	Total Organic Acids, Ce Tenths per Cent Normal per 24 Hours	Plasma Carbon Dioxide, Volume	Height, Cm	Weight, Kg	Body Surface, Square Meters	Age	Sex*	Basal Metabolic Rate	Oxygen Capacity, Ce per 100 Ce	Oxygen Content Arterial Blood, per Cent	Oxygen Saturation Arterial Blood, per Cent	Oxygen Content Venous Blood, (V)	Oxygen Unsaturation Venous Blood, Ce	A—V	Oxygen Intake, Ce per Minute	Cardiac Output, Liters per Minute	Pulse	Cardiac Output per Beat, per Kg Body Weight	Cardiac Output per Beat, Ce per Kg Body Weight
1	5.750	31.7	170.7	50.1	1.53	32	♂	+24.6	18.7	18.4	98.4	14.6	4.1	3.8	269	7.078	82	86.3	1.72
2	4.175	26.1	165.4	53.8	1.59	36	♂	+23.0	17.6	17.4	98.8	13.7	3.9	3.7	267	7.216	92	78.3	1.45
3	4.680	34.7	163.1	59.7	1.64	26	♂	+20.0	19.0	18.8	98.9	15.3	3.7	3.5	305	8.724	108	80.7	1.35
4	4.130	28.1	167.4	55.1	1.61	46	♂	+26.3	13.9	16.7	98.8	13.9	3.0	2.8	253	9.034	86	105.0	1.90
5	3.175	35.7	170.8	54.6	1.63	41	♀	+25.2	19.4	19.2	98.9	16.7	2.7	2.5	254	10.160	94	108.0	1.97
6	4.520	34.9	167.9	72.0	1.80	57	♂	+24.8	18.3	18.1	98.8	15.0	3.3	3.1	291	9.387	92	102.0	1.40
7	2.764	33.0	178.2	63.1	1.85	34	♂	+20.4	20.3	20.0	98.5	17.8	2.5	2.2	304	13.818	110	125.6	1.84
8	3.964	33.0	162.6	70.1	1.76	29	♂	+19.5	17.6	17.1	97.1	15.0	2.6	2.1	269	12.809	98	137.2	1.95
9	4.116	31.2	173.1	65.4	1.78	36	♂	+21.6	16.9	16.6	98.2	13.7	3.2	2.9	294	10.139	114	89.0	1.36
10	3.446	41.7	165.4	63.2	1.69	42	♂	+22.3	15.5	15.3	99.0	11.9	3.6	3.4	275	8.089	78	103.7	1.64
11	5.474	29.8	160.3	62.4	1.65	39	♂	+16.7	16.6	16.4	98.7	13.9	2.7	2.5	263	10.520	96	109.6	1.75
12	3.119	36.7	170.2	64.1	1.74	41	♂	+18.4	19.6	19.1	97.4	15.5	4.1	3.6	274	7.611	79	96.3	1.50
Average								22			98.4		3.2	3.0		9.548	94	121.7	1.67

* In this column, ♂ indicates male, ♀, female

low oxygen unsaturation of venous blood. The basal metabolic rate also is usually increased in this state. These two conditions being present at the same time it is obvious that the increased oxygen intake must be accompanied by an increase in the circulation rate. It is now therefore necessary to note whether, given these two sets of conditions, an increased circulation rate is found by this method. In table 3 are recorded the data demonstrating this phenomenon.

The cases appear to be of the severe type. All patients exhibited a "good" color and the Kussmaul type of respiration. The severity in each case may be judged from the laboratory data recorded in the table, namely, (a) the excretion of large quantities of organic acids and ammonia in the urine, (b) the low carbon dioxide combining power of the plasma, (c) the state of undernutrition, judging from the weight-height-age relationships, and (d) increased metabolic rates. In no case was there any suggestion of heart failure except for the tachycardia. In each case it will be noted that the circulation rate was increased. This appears to give further proof of the reliability of this procedure. In table 4 are briefly summarized the results, and these are compared with the normal.

TABLE 4—*Maximum, Minimum and Average Cardiac Outputs in Normal Persons and in Diabetic Patients with Acidosis*

	Subjects	Average	Maximum	Minimum
Normal		6304.0	7531.0	5052.0
Diabetic		9348.0	13818.0	7078.0

Because of these findings, this method was employed in a series of cases of hyperthyroidism. For comparative purposes hyperthyroid subjects were chosen whose basal metabolic rates, with few exceptions, approximated those found in the series of diabetic cases studied. The basal metabolic rates in fifteen of the twenty cases ranged between plus 15 and plus 36 per cent. All cases belonged to the exophthalmic goiter or toxic hyperplastic group. In no case was there evidence suggestive of heart failure other than tachycardia.

The procedure in this study was simplified by making no actual observations on arterial blood. This appeared justifiable. In the absence of pulmonary congestion or heart lesions suggesting the presence of the latter (mitral stenosis) or congenital anatomic defects, it may reasonably be assumed, as shown by numerous workers, that the arterial blood is fairly completely saturated with oxygen. In ten normal subjects we found that the average saturation of the arterial blood was 95.4 per cent, this agrees very closely with the results of other workers. (Higher values were found in the diabetic series.) The combined data are recorded in table 5.

TABLE 5—Circulation Rates in Hyperthyroidism

Number	Height, Cm	Weight, Kg	Body Surface, Square Meters	Age	Sex*	Basal Metabolic Rate, per Cent Above Normal	Oxygen Capacity, Cc per 100 Cc	Oxygen Content Arterial Blood (A)	Oxygen Content Venous Blood (V)	Oxygen Unsat- uration Venous Blood, Cc	A—V	Oxygen Intake, Cc per Minute	Cardiac Output, Cc per Minute	Pulse	Cardiac Output, Cc per Beat	Cardiac Output per Beat, Cc per Kg Body Weight
1	160.0	49.1	1.49	70	♂	31	16.5	15.7†	9.5	7.0	6.2	240	3,871	106	36.5	0.74
2	163.0	45.3	1.46	47	♀	37	15.7	15.0	11.1	13	3.6	250	6,944	112	62.0	1.36
3	171.0	66.8	1.78	17	♂	19	17.2	16.4	10.7	5.7	6.5	290	5,087	108	47.1	0.701
4	169.6	61.9	1.72	55	♂	40	14.9	14.2	9.8	3.4	5.1	316	7,182	136	52.8	0.85
5	163.3	45.3	1.46	26	♀	32	16.1	15.3	11.2	3.1	4.9	290	7,073	109	64.9	1.43
6	158.6	46.8	1.45	47	♀	34	16.2	15.4	11.6	3.8	4.6	213	6,395	104	61.5	1.31
7	151.8	66.1	1.65	25	♀	32	14.8	14.1	9.8	4.3	5.0	280	6,512	118	55.1	0.83
8	165.1	52.3	1.56	58	♂	55	16.5	15.7	11.3	4.4	5.2	315	7,150	110	65.1	1.24
9	153.4	69.7	1.68	64	♀	26	18.0	17.2	14.0	3.2	4.0	250	7,812	114	68.5	0.98
10	175.2	67.4	1.81	40	♂	36	13.9	13.2	9.1	4.8	4.1	328	8,000	116	68.9	1.02
11	155.0	55.8	1.54	37	♂	16	15.8	15.1	11.5	4.3	3.6	245	6,805	114	59.6	1.07
12	164.8	53.9	1.59	23	♂	24	15.9	15.2	11.5	4.4	3.7	270	7,297	100	73.0	1.35
13	157.7	52.1	1.51	20	♂	36	17.3	16.5	11.1	6.2	5.4	264	4,889	112	43.6	0.83
14	175.1	52.7	1.64	63	♂	32	16.4	15.6	10.7	5.7	4.9	275	5,612	120	46.7	0.88
15	155.1	43.9	1.30	25	♀	41	15.8	15.1	12.0	3.8	3.1	213	8,161	117	69.8	1.59
16	162.8	44.4	1.44	22	♂	22	14.9	14.2	10.5	4.4	3.7	241	6,513	109	59.7	1.34
17	161.7	74.4	1.81	24	♂	12	15.6	14.9	9.1	6.5	5.8	279	4,810	113	42.6	0.57
18	163.4	46.8	1.48	26	♀	40	16.4	15.6	9.5	6.9	6.1	282	4,623	124	37.3	0.80
19	168.2	54.2	1.61	23	♂	32	17.1	16.3	9.5	7.6	6.8	292	4,294	118	36.4	0.67
20	155.3	53.6	1.54	37	♂	24	16.0	15.2	10.9	5.1	4.3	262	6,093	110	55.4	0.99
Average																1.02

* In this column, ♂ indicates male, ♀, female

† Arterial blood assumed to be 95.4 per cent saturated

RESULTS

It will be noted that in each case in this series, with one exception, the volume output of the heart per beat was diminished. As just stated, in no case was there any other evidence suggestive of heart failure, with the exception of the tachycardia. The average output per beat was 55.3. The maximum and minimum values were 73 and 36.4, respectively. It would therefore appear that all these patients had some heart failure. A comparative study of the pulse rate, metabolic rate ratios and cardiac outputs per kilogram of body weight in the diabetic and hyperthyroid cases tends to corroborate this finding. For comparative purposes only those cases of hyperthyroidism with metabolic rates not greater than the maximum found in the diabetic cases are now considered. Table 6 shows the relation between the average pulse rate and average metabolic rate.

TABLE 6—*Relation Between Average Pulse and Average Metabolic Rates*

	Hyperthyroidism	Diabetes With Acidosis
Average pulse rate per minute	110	94
Average metabolic rate (increase above normal, per cent)	20	22

Since the average basal metabolic rates in both series of cases were approximately the same, it appears reasonable to assume that some factor other than increased metabolism must account for the excess increase in pulse rate in the cases of hyperthyroidism. The pulse rate = metabolic rate ratio incidentally offers further evidence, if necessary, of the value of the pulse rate in determining the presence of heart failure.

Further evidence of heart failure in these cases of hyperthyroidism is found in a comparative study of the circulation rates of the normal, diabetic and hyperthyroid subjects. Table 4 shows the influence of work (increased basal metabolic rate) on circulation rate. In the cases of diabetes with acidosis with an average increase of 22 per cent in the basal metabolic rate and no heart failure the average volume output of blood per minute increased about 50 per cent. In the cases of hyperthyroidism with a corresponding increase in basal metabolic rate the average volume output per minute approached only that found in the normal resting person. The average volume output per minute was 6.345 liters. It will also be noted (tables 3 and 5) that, unlike in the cases of diabetes, the majority of the circulation rates noted in hyperthyroidism have fallen below Henderson's⁴ estimate of the normal cardiac output, namely, 1.5 to 2.0 cc per kilogram of body weight per beat. In the absence of other clinical evidence of heart failure, the clinical value of such a study as the foregoing is obvious.

4 Henderson, Y. *Physiological Rev* 3 165 (April) 1923

ROENTGEN-RAY THERAPY IN ERYSIPELAS¹

E S PLATOU, M D

AND

LEO RIGLER, M D

MINNEAPOLIS

There probably are few diseases known to man which have caused as much speculation regarding their treatment as erysipelas. Standard textbooks and current medical literature allude to many forms of therapy, among which are well known local applications such as sulfonated bitumen, N F, zinc stearate, magnesium sulphate, alcohol glycerin, mercuriochrome-220 soluble, phenol, lead water, mercuric chloride, picric acid and iodine in various combinations. In addition whole blood, serums, leukocytic extracts and vaccine have all been exploited. Recently Alquier¹ and others have advocated the use of ultraviolet radiation. The multiplicity and variability in methods of treatment in a given disease probably indicate an uncertainty as to the value of all of these therapeutic procedures and the lack of uniform success following their employment only stresses the fact that the disease in question is more or less self limited. Erysipelas stands out as a striking example of this group of diseases, a fact that is quite well accepted.

In view of these numerous and varied attempts in the treatment of erysipelas it is rather singular that so little attention has been paid to the use of roentgen rays, particularly since satisfactory results have been obtained by this procedure. Hesse² and Schrader³ reported encouraging results by the method but had no control cases and used comparatively small repeated doses. Occasional isolated cases are mentioned⁴ in the American literature in connection with groups of pyodermias that have been subjected to roentgen ray. Platou⁵ and Rothneu⁶ also have treated a number of cases of erysipelas and have been greatly impressed with the rapid improvement after exposure to the roentgen rays.

It is obvious that since erysipelas is a self limited disease any form of treatment to be adjudged effective must be so in a very prompt and definite manner. With this in mind we attempted to give the treatment

¹ From the departments of contagious diseases and roentgenology of the Minneapolis General Hospital and the department of pediatrics of the University of Minnesota Medical School.

1 Alquier, L. *Paris méd* **7** 145 (Aug 18) 1917

2 Hesse, W. *Munchen med Wchnschr* **45** 505, 1918

3 Schrader. *Therap Halbmonatsch* **35** 600, 1918

4 Lawson, J D. *Radiology* **6** 153 (Feb) 1926. Hodges, F M. *Am J Roentgenol* **11** 442 (May) 1924

5 Platou, L S. Personal communication to the author

6 Rothneu. Personal communication to the author

over as short a period and as soon as possible after the onset of the disease, hoping that such a procedure would eliminate to some extent the factor of natural improvement. It is apparent that the interpretation of results of a course of roentgen-ray treatments extending over a period of a week or two is always questionable whereas a sharp improvement occurring within one or two days after the administration of any therapy is much more convincing as to its efficacy. For this reason in our cases only one dose of roentgen rays was given and in most cases no other form of therapy was used thereafter except sedatives and analgesics. In the first few cases, our results were somewhat mediocre and it was soon apparent that a larger roentgen-ray dose would be necessary. The technic as finally evolved was as follows:

The facial cases were divided into four areas of exposure: one anterior, over the face and forehead, one on each lateral surface of the face and neck, including the ear, and one on the scalp. The first three areas were always treated regardless of whether they were all involved or not, in the hope of preventing a spreading of the disease to the normal areas. The area over the scalp was treated only when invasion or threatened invasion of it was in process. No protection was used except over the eyebrows. A distance of 10 inches from the tube to the skin of the patient was used over all the areas with 2 mm. of aluminum as a filter. The readings were 111 kilovolts (peak), corresponding approximately to a 7 inch spark gap between moderately blunt points, and 5 milliamperes for five minutes over each area. This was considered a dosage sufficient to produce a very mild erythema when the oblique radiation from each area was taken into account. Over the scalp the dosage was reduced to four minutes to avoid any possibility of producing permanent epilation. Only one treatment was given, all the areas being exposed on the one occasion. In the cases of erysipelas in other parts of the body the affected area, together with a large border of normal skin around it, was treated in the same way, the part to be treated being divided into contiguous areas of approximately 300 sq. cm.

Realizing that mere clinical impressions might lead to erroneous conclusions and that such impressions account for many of the avowed cures, we formulated comparative charts for the tabulating of important clinical data. Careful records were then kept of the patients who received roentgen-ray therapy and those who did not.

Briefly summarized reports of eighteen patients who were treated by iced magnesium sulphate and glycerin packs—the usual routine procedure—are given in table 1.

These eighteen patients were admitted to the hospital in the eight months just prior to the institution of the radiation therapy. They were taken in chronologic order and the only cases eliminated were those in which so many complicating factors were present before the onset of

TABLE 1—Data from Eighteen Patients with Erysipelas Treated by Iced Magnesium Sulphate and Glycerin Packs

Case	Age	Duration at Time of Treatment, Days	Temper- ature	Extent of Infection	Degree of Infection	Time from Treatment to Normal Temperature, Days	Time to Normal Symptoms, Days	Extension After Treatment	Complica- tions and Sequelae	Duration from Treatment to Cure, Days	Duration Whole Illness, Days
1	43	7	102.0	Face only	Severe	5	5	Over neck	Death	7	10
2	43	3	104.0	Forehead	Severe	3	5	Ears	Albuminuria	5	6
3	60	1	100.0	Face, scalp	Mild	4	4	No	None	7	14
4	62	4	103.4	Cheek, forehead	Mild	8	1	Left elbow	Albuminuria	6	13
5	61	7	98.0	Cheek, cheek	Mild	2	3	Ears	None	4	4
6	60	7	101.0	Ear, cheek	Moderate	9*	8	Over eye	None	5	12
7	42	3	104.0	Face, ear	Severe	7	2	Right ear	Gangrene, death	9	11
8	32	6	102.4	Face, ears	Moderate	2	9	Back, arm	Tonsillitis	8	15
9	65	32	102.0	Face neck	Moderate	7	2	Back, arm, scalp	None	21	24
10	32	7	104.2	Face	Mild	7	3	Ears, arm, scalp	None	5	7
11	38	3	102.2	Face	Moderate	3	3	Ear	None	4	6
12	68	2	Nor	Nose	Mild	11	12	No	Death	17	22
13	70	2	101.0	Face, ear, scalp	Mild	4	5	Neck, back, buttocks	None	7	10
14	45	2	100.0	Nose, cheek	Moderate	3	3	Ear	None	8	9
15	54	5	102.8	Forehead, cheek, ears	Severe	8	8	Back, arms	Death	8	22
16	22	3	103.8	Nose, cheek, forehead	Severe	4	5	Face	None	7	10
17	47	3	104.0	Face, elbow	Mild	8	8	Scalp, neck	None	8	9
18	20	1	101.0	Cheek	Mild	8	8	Face, ear, neck	None	8	9

the erysipelas as to make it difficult to evaluate the results of the treatment. In table 2 are given similar reports of twenty-three cases, also unselected, which were treated with roentgen rays. The data in the two groups were selected on precisely the same basis. As the second group followed the first in chronologic order, both were studied in the contagious disease department of the Minneapolis General Hospital, and both were treated under the same conditions, and thus may be compared fairly well as to results.

The tables are self explanatory but certain important facts should be emphasized. In the group of eighteen cases (table 1) treated in the usual manner there were four deaths. Only one death (case 22) occurred in the twenty-three cases (table 2) treated with roentgen rays. This occurred in a child who was just recovering from measles, and had evidence of bronchopneumonia at the time the treatment was given. In this child the local manifestations of the erysipelas disappeared within thirty hours after the treatment but the toxic signs persisted with eventual death, due, in our opinion, to bronchopneumonia. In the group of control cases, the period of elevated temperature varied from two to eleven days, the average being five days. In contrast to this, almost all the patients treated by our method (roentgen ray) had a normal temperature in from one to two days (range 1-3 days) after the treatment was given. The temperature in the majority of cases dropped to normal within twenty-four hours. Likewise, the symptoms, such as pain, toxicity and general malaise, disappeared within one to two days after the roentgen-ray treatment, whereas in cases treated by local application a longer period was required.

Practically all the control cases showed a spreading of the process to contiguous parts of the skin after the treatment was begun. Of the patients treated with roentgen rays only, one patient (case 11) showed extension and this was very slight. Likewise, there was only one case (case 4) in this series in which a complication occurred, a suppurative cervical adenitis which healed rapidly after incision. In case 16, otitis media was present before the onset of the erysipelas and consequently it was not considered as being a complication. In this case the temperature remained elevated after the disappearance of the erysipelas owing, no doubt, to the otitis media. Three patients (cases 19, 20 and 21) treated with roentgen rays did not show such satisfactory results but they are not considered with the remainder of the group because of certain complicating factors existing before the treatment was given or because other forms of treatment had been instituted previously. Two of them (cases 19 and 20) were inadequately treated as they were among the first patients on whom the roentgen-ray method was used. Case 20 had a puerperal infection before the onset of the erysipelas and developed septicemia, which may have been due to the pelvic disease, mercuro-

TABLE 2—Data from Twenty-Three Patients with Erysipelas Treated by Roentgen Rays

Case*	Age	Duration at Time of Treatment, Days	Temper- ature	Extent of Infection	Degree of Infection	Time from Treatment to Normal Temper- ature, Days	Time to Normal Symptoms, Days	Extension After Treatment	Complica- tions and Sequelae	Duration from Treatment to Cure, Days	Duration Whole Illness, Days
1	44	6	101.4	Nose, ears, cheeks	Moderate	1	1	No	None	4	10
2	60	17	103.4	Face, ears, forehead	Severe	1	1	No	None	2	19
3	60	2	103.4	Face, ears	Severe	1	1	No	None	3	5
4	44	8	Nor	Face	Mild	2	2	No	Abscess †	3	11
5	38	2	102.0	Face, ears, spreading	Moderate	1	1	No	None	2	4
6	57	2	100.4	Face, forehead	Moderate	1	1	No	None	2	4
7	55	4	101.0	Cheek, ear	Moderate	1	1	No	None	2	6
8	59	5	99.2	Face, ears	Moderate	2	2	No	None	3	8
9	39	2	Nor	Face, forehead	Mild	1	1	No	None	3	5
10	34	2	Nor	Nose, cheeks	Mild	1	1	No	None	2	4
11	37	6	99.4	Face	Mild	1	1	Slight to neck	None	3	9
12	27	2	100.4	Nose, cheek	Moderate	1	1½	No	None	5	7
13	26	2	101.0	Nose	Mild	1	1	No	None	3	5
14	43	3	101.0	Nose, cheeks	Moderate	1½	1	No	None	4	7
15	65	2	103.0	Face	Severe	1½	1	No	None	3	5
16	2	5	102.2	Face, ear	Moderate	1	1½	No	Otitis †	2	7
17	30	2	102.0	Face, ear	Moderate	1	2	No	None	3	5
18	27	3	Nor	Face	Mild	1	1	No	None	2	5
19	24	6	104.0	Face, spreading	Severe	4	2	Scalp, neck	Arthritis	4	10
20	22	2	104.6	Buttocks, perineum	Severe	3	2	Legs	Septicemia	5	8
21	25	3	102.0	Face	Moderate	3	2	Scalp	Infected eye	5	8
22	11 mo	2	104.4	Face, scalp	Extreme	1½	2	None	Pneumonia, death	4	18
23	26	14	102.2	Face	Severe	1½	2	No	None	4	18

* In case 19 inadequate treatment was given and had to be repeated, ice packs also were used. In case 20 the patient had a puerperal infection and septicemia developed, mercuriodichromate-220 soluble also was used, inadequate treatment was given. In case 21 inadequate treatment was given and magnesium sulphate packs were used. The bronchopneumonia in case 22 was a complication of measles which the patient had just passed through, it was present before treatment. Patient 23 was treated in the routine manner without improvement for seven days before irradiation therapy was given.

† Thus was a suppurating gland which healed after incision.

‡ The otitis media was present before the onset of erysipelas and continued to produce temperature after erysipelas had disappeared.

§ The temperature continued for a long period of time because of puerperal infection and septicemia.

chrome-220 soluble was also used in this case. In cases 19 and 21 ice packs were used together with the roentgen rays, thus confusing the results.

It is difficult to determine the exact time when the disease has completely receded. Some redness and desquamation often persist after the temperature is normal. We considered a patient cured when the redness and swelling were practically gone and the patient was well enough to be up and walking about. Some desquamation usually was still present at this time. Taking this as a criterion, we found that the duration of the disease from the time of roentgen-ray treatment to clinical cure was

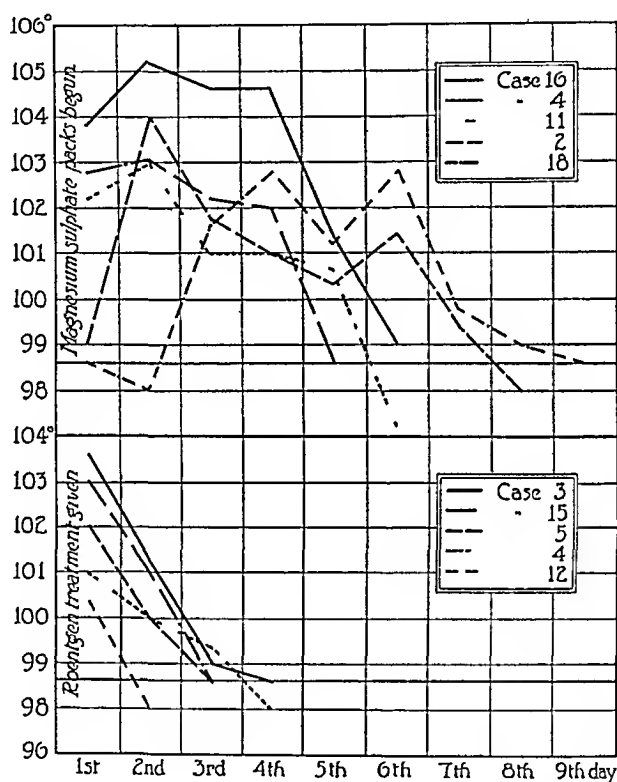


Chart 1—Comparative temperature charts of five average patients treated with magnesium sulphate packs and of five average patients treated with roentgen rays. The unirradiated cases are shown above, the case numbers referring to table 1, the irradiated cases are shown below, the case numbers referring to table 2, the highest temperature only is recorded for each day, the record is begun on the day when treatment was first given and ended on the first day of normal temperature, the lower temperatures and shorter temperature period of the irradiated patients is well shown.

from two to five days, with an average of three days in the irradiated cases. In the routinely treated cases, it varied from four to twenty-one days, with an average of more than nine days. The duration of the whole illness is also given in the tables but has little significance as the duration of the disease at the time of treatment varied so widely.

The temperature record of five average patients treated in the usual manner and five average patients treated with roentgen rays is shown in chart 1. Only the highest temperature of each day is recorded and the chart is begun on the day when the treatment was first given and ended on the day of the first normal temperature. This shows graphically the much milder and shorter course in the irradiated cases. In chart 2 is shown a more detailed temperature record of patient 23 who was given iced magnesium sulphate and glycerin packs for seven days, with spreading of the infection and no relief. One roentgen-ray treatment was then given with a marked change for the better within twenty-four hours. This patient seemed to be much worse at the time the radiation was given than at any previous time.

When these patients were looked at in a general way, without regard to details of temperature and clinical course, it was apparent to all those who were in contact with them, that the patients receiving roentgen-ray

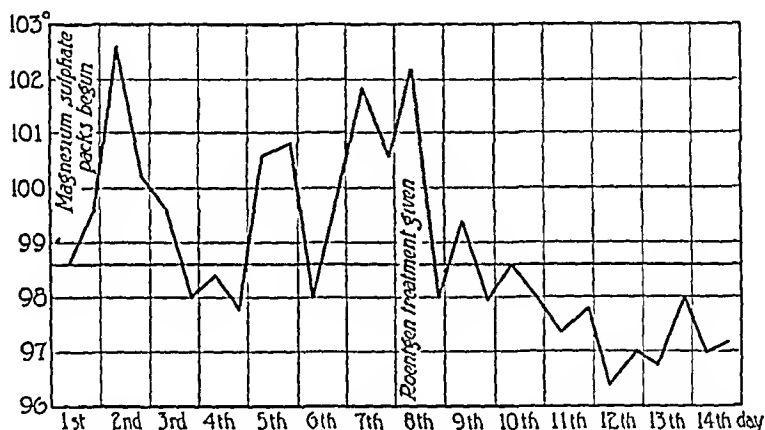


Chart 2—Complete temperature record of patient 23 treated by the usual methods without success followed by roentgen-ray treatment on the eighth day after entrance, the marked change in the course of the temperature is obvious.

treatment improved far more rapidly than the patients receiving routine treatment for erysipelas. Although it is possible that there were more severe cases in the control group than in the irradiated one, nevertheless there were a number of cases with a serious outlook in the latter series. The average age of the two groups did not differ materially. There were a number of patients of advanced age with chronic alcoholism in the group that had received roentgen-ray treatment, in which the prognosis ordinarily would be grave. It was surprising to see how rapidly these patients became well.

The possibility of deleterious effects of the irradiation on the skin or hair must be considered. In no case was there even the slightest tanning of the skin or any other effect that could be assigned to the irradiation. In two cases there was a temporary loss of hair but this may occur following erysipelas of the scalp without irradiation. It appears

that erysipelatous skin is more resistant to irradiation than the normal skin

It is difficult to determine the actual cause of the beneficial effect that we have observed. It appears reasonable to assume that it is due to some change in the circulation, possibly to the capillary effect which has recently been described by Pohle.⁷

SUMMARY AND CONCLUSIONS

The present methods of treatment of erysipelas are distinctly unsatisfactory and accomplish little.

Roentgen-ray therapy applied to the affected part produces a rapid improvement in both the local and the systemic manifestations, with a reduction of temperature to normal in from one to two days.

In a group of cases treated by the routine methods and a similar group treated by roentgen-ray irradiation, the vastly superior results in the irradiated group are shown.

Treatment with the roentgen ray is an effective method for shortening the course and decreasing the morbidity and mortality in erysipelas.

⁷ Pohle, E. A. *Radiology* 6 236, 1926

A MODIFICATION OF THE UREA CONCENTRATION TEST

HAROLD W JONES, M D
AND
ABRAHAM CANTAROW, M D
PHILADELPHIA

Many attempts have been made in recent years to develop a satisfactory test for the urea function of the kidney. Ambard presented his coefficient of urea excretion and F C McLean introduced the McLean index, which utilized the principles of Ambard's formula but simplified them. H MacLean and de Wesselow¹ brought out the urea concentration test. Addis² studied the ratio between the one hour urine urea and the urea in 100 cc of blood and Rabinowitz employed the urea concentration factor $\frac{\text{mg urea in 100 cc urine}}{\text{mg urea in 100 cc blood}}$.

Various investigators have shown that urea excretion in normal persons depends on the blood urea concentration as well as on the renal efficiency and also that the concentration of urea in the urine in normal persons can be increased indefinitely, under conditions compatible with life, by increasing the blood urea concentration. It has been further proved that the volume of water excreted has only a slight effect on urea excretion when the blood urea is not increased and that when the blood urea is increased the volume of water excreted which can influence the excretion of urea is between 2.5 and 6 liters, over this amount no influence is possible.

It is essential that a functional test be readily available as well as accurate in order that it may be useful. The urea concentration test has enjoyed wide use in Great Britain but in this country its use has not been attended with success. The test is available, but its accuracy must be questioned. As described by MacLean and de Wesselow the procedure is as follows:

It is best performed in the morning. The patient is instructed not to eat after dinner the night before so that the stomach may be empty. The bladder is emptied. The patient ingests 150 cc of water flavored with

Read before the section on medicine, College of Physicians, Philadelphia, March, 1925

* From the departments of medicine and physiologic chemistry, Jefferson Medical College Hospital

1 MacLean, H., and de Wesselow, O. L. V. Brit J Exper Path **1** 53 (Feb) 1920

2 Addis, T., and Foster, Marjorie. Concentrating Capacity of Kidney, Arch Int Med **34** 462 (Oct) 1924. Addis, T. Renal Function and Amount of Functioning Tissue, Arch Int Med **30** 378 (Sept) 1922

tincture of orange in which 15 Gm of urea have been dissolved. The urine is collected one and two hours later and if the second specimen is more than 150 cc, a third hour specimen is taken. The urea concentration is measured in the second or third hour specimen by the Marshall urease method. MacLean places the normal concentration at 2 per cent. A mild loss of function is indicated by a concentration of 1.8 per cent.

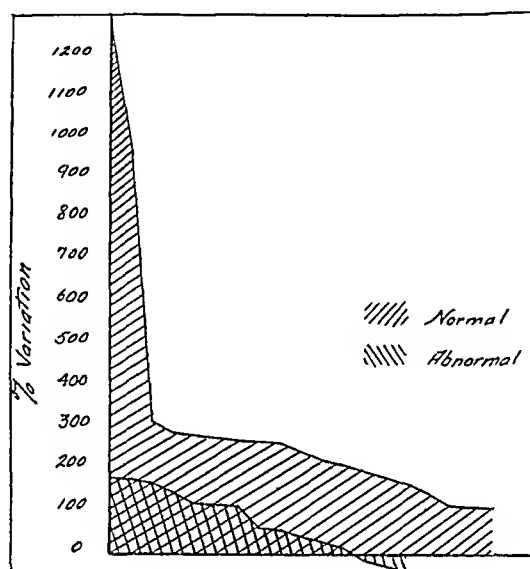


Chart 1—A comparison of the normal and nephritic percentage of variation between the two levels when the resting level is below 1 per cent

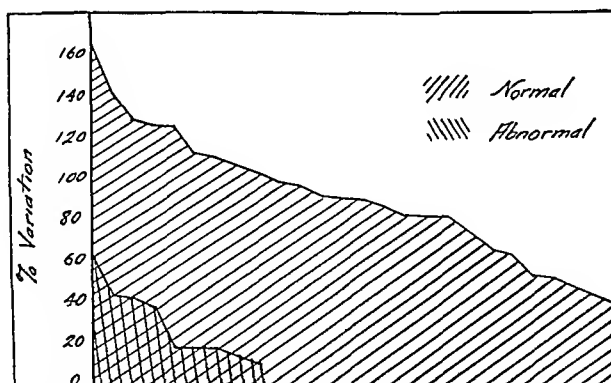


Chart 2—A comparison of the normal and nephritic percentage of variation between the two levels when the resting level is from 1 to 15 per cent

and more severe grades by concentrations of 1.6 per cent or lower. MacLean states that this test yields a more accurate estimation of functional renal impairment than any other. E. Weiss found that the results paralleled those obtained with the phthalein test and stated that it was valuable in the diagnosis of early nephritis.

Like most tests of renal function the urea concentration test fails in certain instances to denote accurately the degree of renal damage and in the following conditions often fails to give evidence of renal damage. In chronic nephritis with salt and water retention it is not uncommon to find a urine urea concentration of 2 per cent or above. Certain patients with symptoms of severe renal damage were studied in whom the urea concentration was 1.5 or 1.6 per cent. The kidneys of these patients at necropsy showed almost complete loss of functioning tissue. The urea concentration should have been much lower. A considerable number of

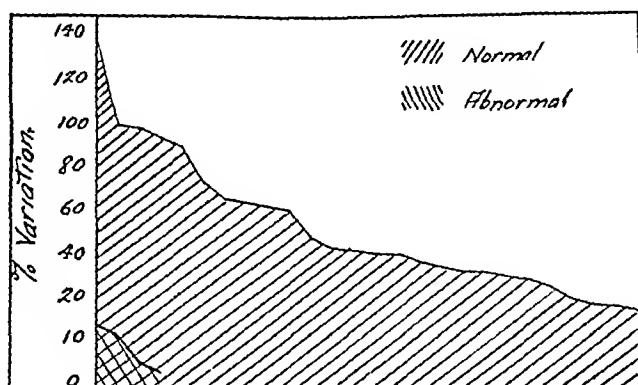


Chart 3—A comparison of the normal and nephritic percentage of variation when the resting level is from 1.5 to 2 per cent

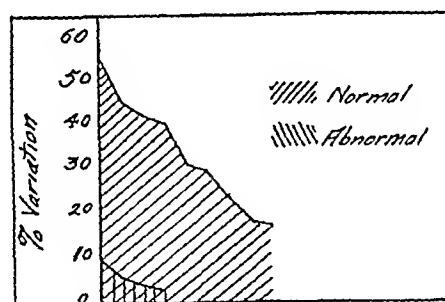


Chart 4—A comparison of the normal and nephritic percentage of variation when the resting level is 2 per cent or above

patients have been studied who had a high blood urea and whose urine urea concentration was 2 per cent. Any test in which the difference between abnormal and normal urine urea varies only by 0.2 per cent must be open to wide possibilities of error.

We concluded from the results obtained with this test that in severe nephritis the urine urea concentration would be almost the same following the ingestion of water alone as that following the ingestion of water plus urea. We felt that there must be a definite response of the normal kidney to the ingestion of urea and that a failure of response might indicate degrees of renal impairment. We termed the urine urea concentra-

Urine and Blood Examinations

Case	Age	Diagnosis	Urine Examinations				Phenol sulphon phthal en, per Cent	Urea Concentration			Blood Chemistry			Condition	
			Quantity, Cc	Specific Gravity	Albumin	Casts		Rest Level, per Cent	Urea Response per Cent	Per centage Variation	Non-protein Nitrogen, Mg	Creatinine	Blood Pressure		
1					+++	Many granular	40	0.23	0.515	121		34	1.9	200-170 130-100	Condition serious on admission stuporous, much improved after two weeks
2	69	Chronic interstitial nephritis	1,500	1.010 to 1.015	+++	Many hyaline and granular	25	0.24	0.52	116	46.2	31.8	1.9	200-170 130-100	Condition serious, headache, dizziness, weakness, unimproved
3	30	Chronic interstitial nephritis	850 to 1,750	1.010 to 1.016	+++	Few hyaline	15	0.288	0.6	111	74.07	48.6	3.128	210-170 140-110	Moderate edema of legs, greatly improved general condition following tonsillectomy
4	21	Chronic nephritis with edema	1,000 to 3,500	1.012 to 1.028	++++	Few hyaline and granular	55	0.35	0.2	-43	54.5	31	2.3	140-90	Severe headache, dyspnea, unimproved
5	43	Chronic interstitial nephritis	2,500 to 3,000	1.004 to 1.010	+++	Many hyaline and granular	35	0.36	0.88	144	45	2.7	1.9	100-150 100-120	Severe headache and dizziness, rapid improvement following tonsillectomy
6	37	Chronic diffuse nephritis, tonsillitis	500 to 1,300	1.010 to 1.023	+++	Few hyaline and granular	25	0.4	0.3	-25	37.7	17.3	1.58	210-146 130-94	Condition good, no severe symptoms, discharged improved
7	17	Chronic interstitial nephritis	600 to 900	1.010 to 1.015	+	0	25	0.492	1.2	177	28.6	13.8	1.56	120-110 70-60	Headache, vomiting, edema, toxic, stuporous on admission, died
8	23	Chronic diffuse nephritis	250 to 500	1.009 to 1.017	+++	Few hyaline and granular	15	0.55	0.6	18	55	38	2.4	180-120	Severe vomiting, polyuria, improved after tonsillectomy
9	31	Chronic interstitial nephritis	2,500 to 4,000	1.002 to 1.012	++++	Many hyaline and granular	40	0.648	0.528	-18	33	20.2	1.8	140-100 90-50	Dyspnea, edema, severe decompensation with passive congestion
10	47	Cardiac decompensation, pulmonary tuberculosis	1,000 to 1,800	1.012	++	Occasional hyaline		0.72	1.14	58				90-50 50-60	Very mild attack of nephritis, discharged well
11	27	Rheumatic fever, acute nephritis	700 to 1,100	1.020 to 1.030	+	0		0.88	1.2	47				120-90	Orthopnea, edema of legs, confusion, passive congestion of liver, improved
12	69	Chronic diffuse nephritis, myocarditis	300 to 2,100	1.010 to 1.030	+	Occasional	25	0.9	1.15	28	27.5	14.16	1.53	210-163 110-78	Edema of feet and face, no subjective symptoms, condition unchanged
13	19	Chronic nephritis with edema	1,000 to 1,500	1.009 to 1.026	+	Few hyaline and granular	15	1	1.2	20	28.56	15.2	1.58	120-60	Greatly edematous and dyspneic rapid improvement on salt free diet
14	17	Chronic parenchymatous nephritis	500 to 1,300	1.014 to 1.025	++++	Many hyaline and granular	20	1	1.2	20	57.1	31	2.12	120-170 80-130	

Urine and Blood Examinations—Continued

15	55	Arteriosclerosis, hypertension	650 to 1,500	1 009 to 1 014	+	Occasional hyaline	45	1 02	1 2	17	40	22 3	17	250-115 120-92	Headache, backache, poor vision much improved on salt-free diet
16	60	Chronic nephritis with edema	600 to 900	1 020 to 1 025	+++	Many hyaline and granular	40	1 17	1 94	65	30 6	22 4	2 16	150-170 100-130	Marked edema on admission, rapid improvement on salt-free diet, lost 25 pounds (11 3 Kg.), edema gone
17	45	Chronic nephritis with edema	1,150 to 2,600	1 014 to 1 030	++	Many hyaline and granular	25	1 2	1 35	12	44 4	26	1 8	180-140 100-70	Edema of feet, ascites, slight dyspnea, edema disappearing, general improvement
18	65	Chronic nephritis, uremia, diabetes	1,000 to 1,200	1 008 to 1 030	+	0	15	1 2	1 68	40	25 8	14 7	1 51	180-130 110-70	Admitted in coma, condition much improved on discharge
19	39	Chronic nephritis, myocarditis, pulmonary tuberculosis	800 to 1,900	1 010 to 1 020	++	Many hyaline and granular	40	1 2	1 75	46	43 6	28	2 1	220-170 150-100	Condition moderately severe, slight decompensation, discharged improved
20	21	Acute nephritis	1,000	1 016 to 1 021	++++	Many hyaline and granular	20	1	1 2	20	29 6	29 6	1 5	145 100	Great edema, condition serious, improved and discharged well
21	46	Myxedema	1,100	1 020 to 1 028	+	0		1 22	1 76	44	28 6	15 2	1 63	170-130 100-80	Discharged improved
22	29	Chronic pulmonary tuberculosis, chronic tonsillitis, chronic nephritis	1,150 to 1,400	1 008 to 1 016	++	Occasional hyaline and granular	40	1 6	1 8	12				160 110	Serious condition, left hospital, unimproved
23	45	Bilateral congenital cystic kidneys		1 008 to 1 015	++	Few hyaline and granular	45	1 6	1 82	14		27		150 100	At postmortem almost complete absence of normal renal tissue
24	62	Chronic diffuse nephritis, perinephritis, pyelonephritis, acute anemia	900 to 1,300	1 020	+	0	45	1 8	1 9	6	49 8	29 2	1 7	130 90	Condition serious, unimproved on discharge
25	17	Acute nephritis, infectious enterocolitis	950 to 1,850	1 008 to 1 015	+	Many hyaline and granular	40	2 37	2 44	3		18		130 95	Severe diarrhea following appendectomy, well on discharge
26	18	Acute tonsillitis, acute nephritis	800 to 1,200	1 023	+++	Occasional hyaline and granular	45	2 42	2 66	10				140-90 60-50	Condition very mild, discharged well after tonsillectomy
27	18	Chronic nephritis, splenic anemia	750 to 8,250	1 010 to 1 018	++	Few granular	30	2 76	2 88	4	28 6	16 43	1 61	80-100 20-40	Serious condition, marked anemia, hemorrhage from gastrointestinal tract
28	26	Acute lead poison	900 to 1,900	1 014 to 1 020	+	0	35	3 54	3 78	6		14 2		140 160 100 98	Severe colic, nausea, vomiting, constipation much improved on discharge
29	31	Mitral stenosis, pulmonary tuberculosis	1,000 to 1,600	1 015 to 1 020	++++	Few hyaline and granular		0 45	1 2	166				120-110 80-60	Moderate decompensation, improved
30	32	Pyelitis, chronic suppurative nephritis	960 to 1,200	1 010 to 1 020	+	0	45	0 48	1 32	175	28 5	16 2	1 57	120-140 80-90	One kidney formerly removed, many pus cells, chills, fever, improving under treatment

tion after water alone "resting level," and after water plus urea "urea response level" The following technic is used

The patient should be instructed to eat nothing after the evening meal

- 7 a m 150 cc of water should be ingested
- 8 a m The first specimen of urine should be collected
- 9 a m The second specimen of urine should be collected
- 9 a m 150 cc of water flavored with tincture of orange in which 15 Gm of urea is dissolved should be ingested
- 10 a m The third specimen of urine is collected
- 11 a m The fourth specimen of urine is collected If the fourth specimen is greater in amount than 150 cc, a fifth specimen (at 12 noon) is collected

The urea concentration in the second and fourth specimens is estimated by the Marshall urease method

Ninety-three normal students and thirty patients with nephritis were studied by this method The results of both the normal and the abnormal cases are divided into five groups

1 Those with a resting level urea concentration between 0 and 0.5 per cent There were four in this group The resting level and the urea response level concentration varied 684 per cent

2 Those with a resting level urea concentration (following water alone) between 0.5 and 1 per cent There were twenty-one in this group The resting level urea concentration and the urea response level urea concentration varied 210 per cent

3 Those with a resting level urea concentration between 1 and 1.5 per cent There were thirty-one in this group The percentage variation was 98 per cent

4 Those between 1.5 and 2 per cent There were twenty-eight in this group The percentage variation was 47.8 per cent

5 Those with a concentration of 2 per cent or more There were nine in this group The percentage variation was 38 per cent

In normal persons, the lower the resting level urea concentration the greater the variation between it and the urea response level concentration The higher the resting level, the less the percentage variation between it and the urea response level

There were seven nephritic cases in group 1 The percentage variation was 90 per cent, in normals it was 684 per cent

There were seven cases in group 2 The percentage variation between the resting level concentration and the urea response level was 30 per cent In normal persons it was 210 per cent

There were nine patients in group 3 with a resting level between 1 and 1.5 per cent The percentage variation was 25.5 per cent and in the normal persons it was 98 per cent

There were three cases in group 4 with a resting level of from 1.5 to 2 per cent The percentage variation was 11 per cent and in normal persons it was 48 per cent

There were four patients in group 5 with a resting level of 2 per cent or above. The percentage variation was 54 per cent and in normal persons it was 38 per cent.

The degree of functional impairment may be proportional to the lessened amount of variation between the two levels. Little variation between the two levels when the resting level concentration is high, between 1.6 and 2 per cent, may be more indicative of renal impairment than a greater percentage of difference when the resting level concentration is low.

In chronic nephritis with water or salt retention the urea concentration may be 2 per cent or above but the functional impairment present is

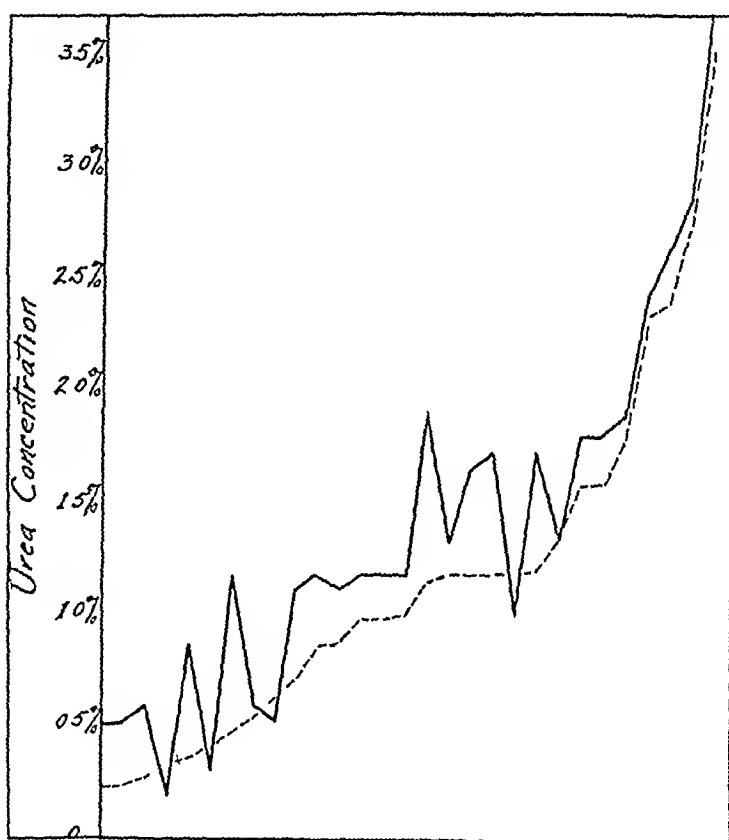


Chart 5—The variation between the two levels in thirty-one patients with nephritis, solid line urea response level, broken line resting level.

shown by a percentage variation between the two levels that is less than normal. Two patients may have concentrations between 1 and 1.5 per cent. In one there may be considerable variation between levels and in the other little or none. The one with the less variation has the greater functional impairment. Functional improvement is shown by an increase in variation between levels in successive tests.

In those cases in which the phthalein test is between 45 and 55 per cent the absence of normal variation between the two levels denotes the presence of functional impairment.

COMMENT

This modification of the urea concentration test is offered to remedy some of the fallacies of the test as heretofore described. The test is readily available and increases the accuracy of the interpretation of changes in urea elimination. If the urea concentration test is to be used it seems better to consider the results from the standpoint of variation between a resting level urea concentration and urea response level concentration than from the urea concentration alone. This report does not include work on any great variety of renal cases and we are not able to state to what extent we may rely on lack of variation to indi-

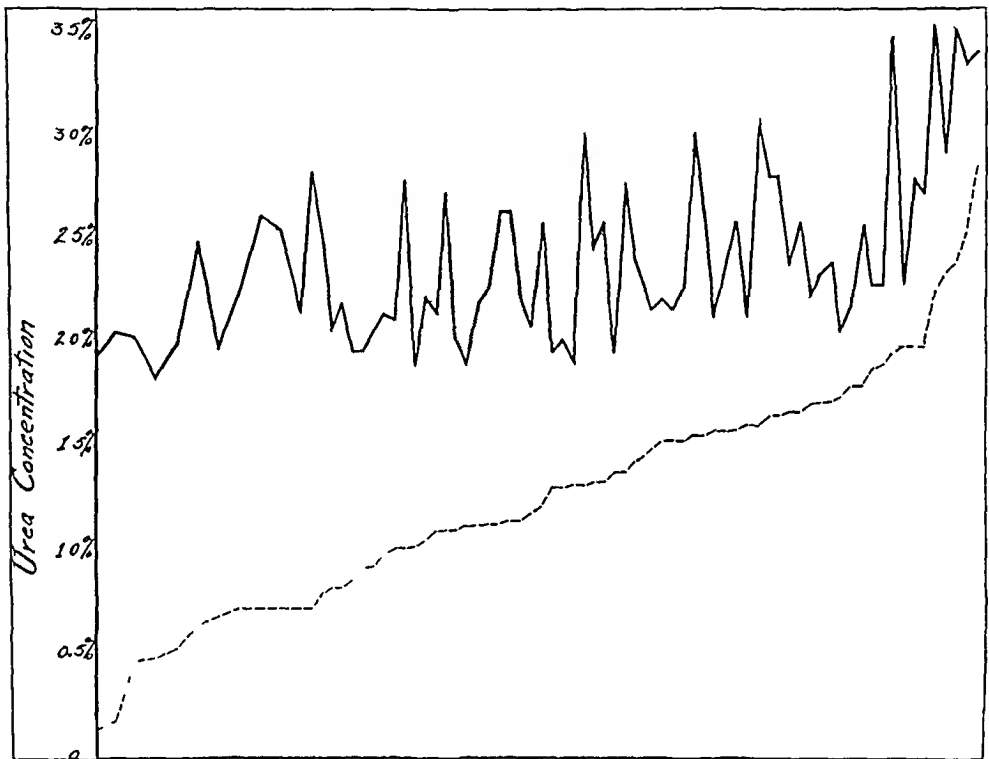


Chart 6—The variation between the two levels in ninety-three normal students, broken line resting level, solid line urea response level

cate varying degrees of renal insufficiency. It seems, however, that the results obtained would indicate that this modification demonstrates with much greater certainty the presence of renal change in a given patient than does the old urea concentration test.

CONCLUSIONS

In a modification of MacLean's urea concentration test the percentage variation between resting level concentration and urea response level concentration is shown to be more significant of renal damage than urea response level concentration alone.

Ninety-three normal persons and thirty patients with nephritis have been studied. They are divided into five groups.

Group 1 includes those with a resting level between 0 and 0.5 per cent. The normals varied 68.4 per cent, the nephritic patients varied 90 per cent.

Group 2 includes those with a resting level concentration between 0.5 and 1 per cent. The normals varied 210 per cent, the nephritic patients varied only 30 per cent.

Group 3 includes those with a resting level urea concentration of from 1 to 1.5 per cent. The normals varied 98 per cent, the nephritic patients varied only 25.5 per cent.

Group 4 includes those with a resting level urea concentration of from 1.5 to 2 per cent. The normals varied 47.8 per cent, the nephritic patients varied 11 per cent.

Group 5 includes those with a resting level urea concentration of 2 per cent or above. The normals varied 38 per cent, the nephritic patients varied 5.4 per cent.

Functional improvement is shown by an increase in variation between the two levels when the test is repeated.

In some instances the phthalein test failed to denote the evident renal impairment, yet the lessened percentage variation was comparable to the functional loss as indicated by physical symptoms.

THE BASAL METABOLISM OF THE JAPANESE *

SEIZABURO OKADA, M D , EIICHI SAKURAI, M D

AND

TOSHIO KAMEDA, M D

TOKYO, JAPAN

As a result of the greatly increased interest in the basal metabolism of human subjects, important contributions on the metabolism of normal Americans and Europeans have been made by various workers, while we have been unable to find any metabolism measurements of normal Japanese until recent years. The first article published on this subject was perhaps that presented by some of us¹ at the regular meeting of the Temporary Beriberi Investigating Committee, Oct 28, 1922, and at the general meeting of the Tokyo Igakkai. The investigation was made under the direction of Prof R Inada on twenty-five students, aged from 22 to 28. The conclusion of this preliminary report was that the basal metabolism of healthy Japanese is quite in accordance with that of Americans and Europeans although the climate, humidity, the conditions of living and physical characteristics are remarkably different from those of Western people.

At an early date Eijkmann,² working in Batavia, could find no significant change in the basal metabolism of the Malays. Using a Zuntz-Geppert apparatus he studied twelve Malay servants accustomed to light work, eleven Europeans living in Batavia, rather heavier than the Malays, and compared these with the normal men studied in Germany by Geppert, Loewy and Magnus-Levy. The oxygen consumption of normal Germans, weighing on the average 62 Kg, was 250.3 cc per minute and that of Malays was 251.5 cc calculated for the same weight, that of Europeans living in Batavia was 245.7 cc.

Fleming,³ in making observations on eight normal Filipinos, reported that all had a basal metabolic rate below the normal standard, the average deviation being —5.3 per cent. The subjects, however, were all surgical convalescents so that these data were for so-called hospital normals.

*From the medical clinic of Prof R Inada, Imperial University of Tokyo, and the medical clinic of Chiba Medical College

1 Okada, S, Sakurai, E, Ibuki, T, and Kabeshima, H. Ikai Jiho, no 1479, Nov 4, 1922

2 Eijkmann, C. Arch f d ges Physiol 64 57, 1896

3 Fleming, W D. J Metab Research 4 105, 1923

Takahira ⁴ in January, 1925, made a report of the basal metabolism of 120 Japanese men and women from the Imperial Nutrition Institute of Japan and concluded that the basal metabolism of the Japanese shows no remarkable difference from that of Europeans and Americans

MacLeod, Crofts and Benedict ⁵ measured the basal metabolism of nine normal Oriental women, seven Chinese and two Japanese, ranging in age from 21 to 29 years, and found that it was in most cases strikingly low, on the average being 104 per cent below the Harris and Benedict prediction standard. Comparisons with the Aub and Du Bois and the Dreyer standards gave essentially the same picture, i e., a persistently low metabolism in these orientals

From the foregoing data it may be seen that there are two different views of the basal metabolism of orientals. On the one hand, it is proved that the basal metabolism of orientals is quite in accordance with that of Western people, others state that a persistently low metabolism exists. It is most important, therefore, to determine this point exactly and whether the Western standards may be applied to the orientals directly or not

OBSERVATIONS AND TECHNIC

Our studies were made on students and nurses who were quite healthy and retained their usual dietary habits and general habits of life. The measurements were made in the postabsorptive condition, that is, at least twelve hours, usually from fourteen to eighteen hours after the last meal, with avoidance of muscular activity and with due regard to the importance of psychic repose. The experiments were made in spring, summer and autumn, i e., in every season except the extremely cold winter. The experimental evidence shows that no essential difference exists in the basal metabolism at different seasons. The physiologic observations included for students the pulse rate, respiration rate and temperature and for nurses vital capacity, systolic and diastolic blood pressure in addition. Records for age, height and weight are made as usual. The surface areas are calculated by the Du Bois height-weight formula ⁶ and partly by using the nomographic chart of Boothby and Sandiford ⁷. In tables 1 and 2 are shown also the surface areas calculated by the formulas derived by Boothby and Sandiford ⁸ from the

⁴ Takahira, H. Report of the Imperial Nutrition Institute of Japan **1** 1, 1925

⁵ MacLeod, G., Crofts, E. E., and Benedict, F. G. *Am J Physiol* **73**:463 (July) 1925

⁶ Du Bois, D., and Du Bois, E. F. *Clinical Colorimetry*, *Arch Int Med* **17**:863 (June) 1916

⁷ Boothby, W. M., and Sandiford, R. B. *Boston M. & S. J* **185** 337 (Sept 22) 1921

⁸ Boothby, W. M., and Sandiford, I. *J Biol Chem* **54** 767 (Dec) 1922

TABLE 1—Data for Normal Males

Case	Age	Height in Cm	Weight in Kg	Surface Area			Pulse Rate	Respi ration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respiratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate	
				Du Bois Height-Weight Formula, Sq Meters	Harris and Benedict Formula, Sq Meters	Harris and Benedict per Cent								Du Bois Standards, per Cent	Harris and Benedict Standards, per Cent
1	23	159.3	44.4	1.42	1.40	+ 17	56	16	147	200	0.74	1,370	40.2	+ 17	+ 39
2	24	158.0	51.4	1.50	1.50	- 82	49	20	159	189	0.84	1,313	36.5	- 82	+ 63
3	28	169.0	47.5	1.46	1.44	- 43	68	9	169	187	0.90	1,325	37.8	- 43	+ 07
4	25	158.8	53.2	1.53	1.53	+ 28	60	12	172	211	0.81	1,405	39.9	+ 10	+ 28
5	25	162.5	56.7	1.67	1.67	+ 03	80	16	188	209	0.90	1,486	38.7	- 20	- 03
6	25	162.5	47.8	1.49	1.47	+ 51	54	12	174	205	0.85	1,438	40.2	+ 18	+ 51
7	24	165.3	46.9	1.46	1.47	- 116	72	17	158	169	0.95	1,216	34.7	- 122	- 116
8	24	162.0	52.3	1.54	1.53	- 18	54	16	160	205	0.78	1,408	38.1	- 36	- 18
9	25	163.2	51.9	1.55	1.53	- 00	74	12	157	203	0.75	1,428	38.4	- 28	- 00
10	24	160.7	47.7	1.47	1.46	+ 39	53	17	165	198	0.83	1,394	39.5	00	+ 39
11	25	157.5	61.3	1.62	1.64	- 06	68	16	185	216	0.86	1,520	39.1	- 10	- 06
12	24	158.9	35.7	1.29	1.27	- 115	72	18	134	209	0.91	1,053	34.0	- 139	- 115
13	25	160.5	55.2	1.57	1.56	- 16	53	15	171	205	0.83	1,436	38.1	- 36	- 16
14	24	165.5	55.2	1.60	1.59	- 82	72	13	166	194	0.86	1,369	35.6	- 98	- 82
15	24	170.9	52.5	1.61	1.60	- 43	66	16	174	209	0.83	1,461	37.8	- 43	- 09
16	24	160.8	54.8	1.57	1.56	+ 03	56	17	189	209	0.90	1,492	39.6	+ 03	+ 21
17	22	158.6	47.6	1.46	1.44	+ 56	78	17	158	214	0.74	1,461	41.7	+ 56	+ 08
18	24	163.5	59.1	1.65	1.64	+ 108	65	17	198	248	0.80	1,712	43.2	+ 93	+ 108
19	24	167.8	49.8	1.49	1.47	+ 115	76	15	182	221	0.82	1,538	43.0	+ 89	+ 115
20	24	163.1	51.1	1.54	1.52	+ 79	60	13	169	219	0.77	1,501	40.6	+ 28	+ 79
21	27	167.6	49.8	1.55	1.52	- 63	53	13	166	185	0.90	1,320	35.5	- 101	- 63
22	23	160.4	46.5	1.45	1.44	- 61	80	16	164	180	0.91	1,270	36.5	- 76	- 61
23	24	161.0	43.9	1.43	1.40	- 03	60	17	150	192	0.79	1,318	38.4	- 28	- 03
24	25	163.5	65.5	1.73	1.74	- 42	56	14	178	226	0.79	1,557	37.5	- 51	- 42
25	25	169.0	55.5	1.56	1.56	+ 66	60	8	179	226	0.79	1,562	43.1	+ 91	+ 66
26	26	160.5	52.8	1.54	1.53	- 159	60	16	125	177	0.71	1,194	32.3	- 182	- 159
27	24	161.5	51.1	1.52	1.51	- 82	63	13	168	182	0.92	1,299	35.6	- 99	- 82
28	24	152.5	46.6	1.41	1.40	- 54	78	18	129	183	0.71	1,238	36.6	- 74	- 54
29	25	177.5	68.5	1.85	1.85	+ 53	59	20	214	264	0.81	1,820	41.0	+ 38	+ 53
30	22	167.1	53.4	1.57	1.57	- 48	62	15	151	212	0.71	1,486	38.1	- 36	- 48
31	22	168.0	48.3	1.47	1.45	- 58	62	14	148	191	0.77	1,312	37.2	- 58	- 58
32	23	162.7	56.0	1.60	1.59	- 31	54	19	158	213	0.74	1,448	37.7	- 46	- 31
33	28	162.2	50.0	1.52	1.50	+ 76	69	14	166	214	0.78	1,481	40.6	+ 28	+ 76
34	24	161.0	53.2	1.55	1.54	- 33	69	13	185	201	0.92	1,436	38.6	- 23	- 33
35	22	162.3	49.0	1.51	1.49	+ 127	76	16	189	231	0.82	1,605	38.6	+ 122	+ 127
36	22	161.5	51.7	1.53	1.52	+ 14	64	15	189	213	0.80	1,669	44.3	+ 13	+ 14
37	22	162.8	50.3	1.52	1.51	+ 06	52	10	173	207	0.84	1,445	39.6	+ 03	+ 06
38	24	166.4	55.0	1.61	1.59	+ 51	74	17	177	229	0.77	1,569	40.6	+ 28	+ 51
39	25	163.3	49.6	1.52	1.50	- 97	59	17	163	229	0.71	1,521	41.7	+ 56	+ 97
40	24	157.5	57.8	1.59	1.59	- 31	68	16	182	203	0.89	1,440	38.0	- 38	+ 31
41	24	155.7	53.2	1.51	1.51	+ 43	58	22	157	220	0.71	1,479	41.2	+ 43	+ 43
42	23	167.2	47.6	1.51	1.49	- 76	70	17	146	188	0.78	1,295	35.7	- 96	- 76
Average	24	161.9	51.85	1.53	1.526	- 20	64	13	169	205	0.82	1,246	38.7	- 20	- 02

TABLE 2—Data for Normal Females

Case	Age	Height in Cm	Weight In Kg	Surface Area			Pulse Rate	Respi- ration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respiratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate	
				Du Bois Sq Meters	Harris and Benedict Formula, Sq Meters	Harris and Benedict Formula, Sq Meters								Du Bois Standards, per Cent	Harris and Benedict Standards, per Cent
1	22	153.1	52.0	1.47	1.50		90	21	151	189	0.80	1,312	37.2	+ 0.5	- 1.5
			52.5	1.47	1.51		62	18	149	179	0.83	1,235	35.0	- 5.4	- 7.6
2	22	150.5	51.0	1.44	1.49		66	19	152	177	0.86	1,220	35.3	- 5.1	- 7.4
			52.5	1.45	1.50		60	17	143	186	0.77	1,271	36.6	- 2.7	- 4.4
3	21	148.0	45.0	1.35	1.42		78	18	132	186	0.71	1,257	38.8	+ 4.8	- 0.3
			44.5	1.35	1.41		72	19	152	187	0.80	1,290	39.8	+ 7.5	+ 2.7
4	22	151.7	62.5	1.61	1.62		60	19	168	233	0.72	1,569	40.6	+ 9.7	+ 9.3
			61.5	1.60	1.61		60	14	168	216	0.78	1,486	38.7	+ 4.3	+ 4.1
5	20	140.6	45.5	1.31	1.41		72	14	147	171	0.86	1,195	38.0	+ 2.7	- 4.9
			45.5	1.31	1.41		80	12	143	152	0.91	1,088	34.6	- 6.5	- 13.4
6	20	147.5	48.5	1.40	1.46		66	14	146	183	0.80	1,237	37.4	+ 1.0	- 3.1
			48.5	1.40	1.46		58	14	143	166	0.86	1,159	34.5	- 6.7	- 10.7
7	21	153.0	40.5	1.33	1.39		60	11	145	175	0.83	1,213	35.9	+ 2.7	- 1.1
8	21	148.8	47.0	1.38	1.44		72	10	120	141	0.85	1,033	31.2	- 15.6	- 19.4
			47.5	1.39	1.44		60	12	107	148	0.72	1,064	31.9	- 13.8	- 17.2
9	21	150.1	47.0	1.39	1.44		78	11	161	178	0.79	1,228	36.8	- 0.5	- 4.3
			47.0	1.39	1.44		66	12	132	181	0.72	1,241	37.2	+ 0.5	- 3.3
10	21	150.8	57.5	1.52	1.56		81	13	177	194	0.81	1,339	36.7	- 0.8	- 3.4
			56.5	1.51	1.55		78	8	152	200	0.76	1,363	37.6	+ 1.6	- 0.9
11	20	149.2	45.5	1.37	1.42		72	17	129	184	0.70	1,240	37.7	+ 1.9	- 2.6
			45.5	1.37	1.42		90	11	163	177	0.92	1,259	38.3	+ 3.5	- 1.1
Average	21	150.5	50.0	1.43	1.47		70	15	146	181	0.81	1,258	36.75	- 0.7	- 3.9

Harris and Benedict formulas⁹ for the prediction of total calories in men and women

The metabolic rates are obtained by the open or gasometer method with analysis of the expired air by the Haldane gas analysis apparatus. Two analyses are made of the expired air, and the results are accepted if they agree within 0.04 per cent for carbon dioxide and 0.06 per cent for oxygen, additional analyses are required if there is a greater discrepancy. Repeated outdoor air analyses are made and a very definite routine, described in detail in the laboratory manual of the technic of basal metabolic determinations of Boothby and Sandiford, has been adopted. The cooperation of the subjects is the important factor to get the basal values. The calmness of the subjects usually was proved by repeated measurements of the expired air of five minutes. If great discrepancy and irregularity of the ventilation rates were observed, additional measurements were made until fairly constant values had been obtained. With nervous and restless subjects this procedure is apt to fail and sometimes it takes many days until consistent results are obtained. In some cases the recording apparatus of Krogh was also used parallel with the gasometer method and the results found to agree closely.

RESULTS

Physical Characteristics—The main observations in this study are shown in the tables. Special consideration should be given to the physical characteristics of the subjects. The normal men were all medical students, ranging in age from 22 to 28, the average age being 24. The average height was 161.9 cm and the average weight, 51.85 Kg. The normal women were all nurses of the college hospital, ranging in age from 20 to 22, the average age being 21. The average height was 150.5 cm and the average weight, 50 Kg. Compared with the average data of Americans of the same age (for example, 172 cm and 64.7 Kg for males, 161.3 cm and 59.1 Kg for females of the Boothby and Sandiford's cases), the relatively small size and shortness of stature of the Japanese are evident. Takahira, who measured with molds, has suggested, however, that the Du Bois height-weight formula for surface area will also be satisfactorily applied to the Japanese. The average surface area for the forty-two normal men, according to the Du Bois height-weight standards, is 1.53 square meters, and according to the Harris and Benedict height-weight standards for men is also 1.53 square meters, for the eleven normal women the Du Bois standards give an average of 1.43 square meters and the Harris and Benedict standards for women 1.47 square meters.

⁹ Harris, J. A., and Benedict, F. G. Carnegie Inst. Washington Pub. 279, 1919.

Physiologic Functions—**Vital Capacity** The vital capacity of eleven women ranged from 216 to 291 liters, being on the average 247 liters. West¹⁰ computes that for women the vital capacity in cubic centimeters divided by the height in centimeters equals 20, and that the vital capacity in liters divided by the body surface in square meters is equal to 2. The Teachers College group (thirty-six women) mentioned by MacLeod, Crofts and Benedict showed ratios of 18.3 and 1.86, respectively. In the case of our subjects the vital capacity divided by the height ranged from 15.2 to 19, the average of the eleven subjects being 16.5. The vital capacity divided by the surface area ranged from 1.61 to a maximum of 2.19, the average for the eleven women being 1.76. Another series of seventy-six women (hospital nurses) showed ratios of 16.9 and 1.82, respectively. Thus, based on these American standards, our subjects showed somewhat low vital capacity.

Blood Pressure The blood pressure of eleven women was determined. The Riva-Rocci sphygmomanometer with the auscultatory method was employed throughout. The systolic pressure ranged from 90 to 113 mm, the average being 101 mm on the right side, on the left side from 80 to 113 mm, the average being 96 mm. The diastolic pressure ranged from 42 to 80 mm, the average being 64 on the right, on the left side from 42 to 77 mm, the average being 61 mm. The average pulse pressure was 37 mm on the right side and 35 mm on the left side.

Pulse Rate The average pulse rate of the forty-two men studied was 64 beats per minute, the minimum being 52 and the maximum 80. The average pulse rate of the eleven women was 70, the minimum being 58 and the maximum 90. In general the pulse rates of women are higher than those of men. The average pulse rate in a series of normal cases studied by Gephart and Du Bois¹¹ for men was 62 and for ninety women, whose metabolism data were analyzed by Harris and Benedict, 68. The average pulse rates of eighty-nine normal men and sixty-eight women observed by Benedict and Emmes¹² were 61 and 69, respectively. In view of the fact that our patients were all relatively young, the pulse rates of these Japanese practically coincide with those of the Americans.

Respiration Rate The average respiration rate of forty-two men was 13 and that of eleven women was 15. When the subjects

10 West, H. F. Clinical Studies on Respiration, Comparison of Various Standards for Normal Vital Capacity of the Lungs, *Arch Int Med* **25** 306 (March) 1920.

11 Gephart, F. C., and Du Bois, E. F. Clinical Colorimetry. The Determination of the Basal Metabolism of Normal Men and the Effect of Food, *Arch Int Med* **15** 835 (May) 1915.

12 Benedict, F. G., and Emmes, L. E. *J Biol Chem* **20** 253, 1915.

were breathing normally in the room, without masks, the rate was 15 and 17, respectively. Sometimes a pronounced effect of the use of the respiration appliance on the respiration rate was observed. The respiration rate of 8 was noted with subject 25 (male), when this subject was breathing normally in the room, without mask, the rate was 11 respirations a minute. A pronounced alteration in the respiration rate when the mask is used, usually a slowing of the rate, has frequently been noted by us, this is not infrequently noted in the literature.

Temperature The body temperature of the males ranged from 36 to 37.1 C, the average being 36.4 C, that of the females ranged from 35.5 to 36.6 C, the average being 36 C. The temperature of the room when the experiment was carried out ranged from 29 to 14.4 C, the average being 22.8 C in males, in females from 27.2 to 11.4 C, the average being 17.6 C.

Basal Metabolism In males the oxygen consumption varied from 148 cc in subject 12 to 264 cc per minute in subject 29, the average being 205 cc. The carbon dioxide production varied from 125 cc in subject 26 to 214 cc in subject 29, the average being 169 cc. The respiratory quotient ranged from 0.71 to 0.95, the average being 0.82. In females the oxygen consumption varied from 141 cc in subject 8 to 233 cc in subject 4, the average being 181 cc. The carbon dioxide production varied from 107 cc in subject 8 to 168 cc in subject 4, the average being 146 cc. The respiratory quotient ranged from 0.70 to 0.94, the average being 0.81. The range of the total twenty-four hour heat production in males was from 1,052 calories in subject 12 to 1,605 calories in subject 35, the average being 1,426 calories, in females from 1,033 calories in subject 8 to 1,569 calories in subject 4, the average being 1,258 calories. As has already been pointed out, the normal American subjects are taller and heavier on the average than the Japanese, so the total heat production of our subjects is not directly comparable with that of western normals. The basal heat production for males as predicted by Harris and Benedict is

$$h = 66.4730 + 13.7516w + 5.0033s - 6.7550a$$

and for females is

$$h = 655.0955 + 9.5634w + 1.8496s - 4.6756a,$$

in which

a = age in years

h = heat production per twenty-four hours

w = weight in kilograms

s = stature in centimeters

By means of this prediction formula we have predicted from the age, height and weight of our subjects their total twenty-four hour metabo-

lism and compared it with that actually measured. The deviations from these predictions expressed in percentage are also recorded in tables. In this comparison most cases except two, one male and one female, show deviations less than ± 15 per cent from the standards, i. e., 96 per cent of all cases are within ± 15 per cent, forty-six cases, 87 per cent, are within ± 10 per cent. In males nearly the same number are plus and minus while in females more cases are somewhat less than the predicted metabolism. The average heat production predicted by Harris and Benedict is 1,429 calories for males and 1,309 calories for females. The average deviation of the actually measured metabolism from the standards is therefore -0.2 per cent for males and -3.9 per cent for females. The standards of Harris and Benedict for women are believed to be 5 per cent too high, therefore our results coincide fairly well with the commonly accepted standards for Americans.

The standards of Aub and Du Bois¹³ for the age range of our subjects, that is, between 20 and 30 years, is 39.5 calories per square meter of body surface per hour for males and 37 calories for females. A comparison of the heat production per square meter of body surface per hour with the Aub and Du Bois standards shows 98 per cent of the whole number of cases to be within ± 15 per cent, 89 per cent within ± 10 per cent of the standards. The average heat production in males per square meter per hour is 38.7 calories, -2 per cent, and of female cases is 36.75 calories, -0.7 per cent of the standards. King¹⁴ proposed to use the carbon dioxide elimination as an index to basal metabolism. For the range of age from 20 to 30 years the normal figures are 12.98 Gm for men and 11.95 Gm for women per square meter of body surface per hour. The average carbon dioxide elimination of our males was 12.87 Gm and of the females, 11.89 Gm per square meter per hour. The percentage deviation of the former from the standards was therefore -0.8 and of the latter, -0.5 .

Krogh,¹⁵ Benedict and others consider that the present standards are probably from 4 to 5 per cent or more too high. Sanborn¹⁶ in his work on basal metabolism has presented a table containing the Du Bois normal standards with 1.8 calories arbitrarily deducted. A comparison of the heat production of our cases with this modified standard also shows nearly the same percentage of cases to be within ± 15 per cent of the original standards.

It is a well known fact that prolonged starvation causes a marked diminution of the basal metabolism. It is also stated by some authors

13 Aub, J. C., and Du Bois, E. F. Metabolism of Old Men, *Arch. Int. Med.* **19** 823 (May) 1917.

14 King, J. T., Jr., and Pearl, R. *Bull. Johns Hopkins Hosp.* **32** 277 (Sept.) 1921. King, J. T., Jr. *Basal Metabolism*, 1924.

15 Krogh, A. *Boston M. & S. J.* **189** 313 (Aug. 30) 1923.

16 Sanborn. *Basal Metabolism*, 1922.

TABLE 3—Data for Normal Males Using Different Diets on the Previous Day

PART 1

Onset	Age	Date	Height in Cm	Surface Area			Respi- ration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respi- ratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate		Diet of Pre- vious Day, Calories per Kg of Body Weight
				Weight in Kg	Height Formula, Sq Meters	Pulse Rate							Du Bois Standards, per Cent	Harris and Benedict Standards, per Cent	
1	24	3/13 3/14	161.5	51.1 51.2	1.52 1.53	68 60	13 15	168 176	182 218	0.92 0.81	1,299 1,506	35.6 41.0	-9.9 +3.8	-8.2 +6.4	Usual 40.0
2	24	3/27 3/28	152.5	46.8 46.6	1.41 1.41	78 62	18 19	129 148	183 187	0.71 0.79	1,238 1,283	36.6 37.9	-7.4 -4.1	-5.4 -1.8	Usual 40.0
3	25	3/28 3/29	177.5	68.5 68.5	1.85 1.85	59 52	20 18	214 218	264 274	0.81 0.79	1,820 1,887	41.0 42.5	+3.8 +7.6	+5.3 +9.2	Usual 40.0
4	22	3/29 3/30	167.1	53.4 54.2	1.57 1.58	62 62	15 15	151 160	212 193	0.71 0.83	1,436 1,345	38.1 35.7	-3.6 -9.6	-4.3 -10.3	Usual 40.0
5	22	4/5 4/6	158.0	48.3 48.7	1.47 1.47	62 59	14 15	148 164	191 199	0.77 0.82	1,312 1,379	37.2 39.1	-5.8 -1.0	-5.3 -0.4	Usual 40.0
6	23	4/6 4/7	162.7	56.0 56.0	1.60 1.60	56 56	19 19	158 193	213 227	0.74 0.85	1,448 1,590	37.7 41.4	-4.6 +4.8	-3.1 +6.3	Usual 40.0
7	28	4/7 4/8	162.2	50.0 50.2	1.52 1.52	69 64	14 12	166 170	214 196	0.78 0.87	1,481 1,382	40.6 37.9	+2.8 -4.1	+7.6 +0.4	Usual 40.0
8	24	4/9 4/10	161.0	53.2 53.1	1.55 1.55	69 62	13 13	185 183	201 221	0.92 0.83	1,485 1,533	38.6 41.2	-2.3 +4.3	-3.3 +3.2	Usual 40.0
9	22	4/12 4/13	162.3	49.6 49.8	1.51 1.51	76 65	16 16	189 185	231 218	0.82 0.85	1,605 1,522	44.3 42.0	+12.2 +6.3	+12.7 +6.9	Usual 40.0
10	22	4/22 4/23	161.5	51.7 51.8	1.53 1.53	64 58	15 14	171 158	213 205	0.80 0.77	1,469 1,368	40.0 38.3	+1.3 -3.0	+1.4 -5.6	Usual 40.0
11	24	6/8 6/10	157.5	57.8 57.0	1.58 1.57	68 72	16 15	182 180	208 206	0.89 0.87	1,440 1,447	38.0 38.4	-3.8 -2.8	-3.1 -2.0	Usual 40.0
Average of usual diet															
Average of 40 calories per kilogram of body weight															
													-1.5	-0.4	
													0.0	+1.2	

PART 2

1	22	5/13 5/14 5/15	162.8	50.3 49.9 49.8	1.52 1.52 1.52	52 50 54	10 11 12	173 173 160	207 206 213	0.81 0.81 0.75	1.415 1.434 1.452	39.6 39.3 39.8	+ 0.3 - 0.5 + 0.8	+ 0.6 - 0.1 + 1.1	Usual 30.0 40.0
2	24	6/ 3 6/ 4 6/ 5	166.4	55.0 55.5 55.7	1.61 1.61 1.61	74 58 54	17 15 15	177 179 180	229 226 221	0.77 0.79 0.80	1.569 1.553 1.519	40.6 40.2 40.1	+ 2.8 + 1.8 + 1.5	+ 5.1 + 4.0 + 3.7	Usual 30.0 40.0
3	25	6/ 3 6/ 4 6/ 5	163.3	49.6 50.2 50.7	1.52 1.52 1.53	59 49 57	17 17 17	163 160 165	229 201 193	0.71 0.78 0.83	1.521 1.401 1.375	41.7 38.4 37.7	+ 5.6 - 2.8 - 4.5	+ 9.7 + 1.1 - 0.8	Usual 30.0 40.0
4	24	6/10 6/11 6/12	157.7	53.2 53.8 53.8	1.51 1.52 1.52	68 42 70	22 18 17	157 165 173	220 205 193	0.71 0.80 0.87	1.479 1.412 1.390	41.2 38.7 38.1	+ 4.3 - 2.0 - 3.5	+ 4.5 - 0.2 - 1.7	Usual 30.0 40.0
5	23	6/17 6/18 6/19	167.2	47.6 47.3 47.4	1.52 1.51 1.51	70 53 60	17 15 18	146 150 151	183 187 189	0.78 0.80 0.80	1.295 1.234 1.305	35.5 35.7 36.0	-10.1 - 9.6 - 8.8	- 7.6 - 7.4 - 6.6	Usual 30.0 40.0
Average of usual diet				51.1	1.54	63	17	163	215	0.76	1.462	39.7	+ 0.5	+ 2.5	
Average of 30 calories				51.3	1.54	51	15	165	206	0.80	1.419	38.5	- 2.4	- 0.5	
Average of 40 calories				51.5	1.54	54	16	167	204	0.82	1.414	38.3	- 3.0	- 0.8	

The diet of 40 calories per kilogram when the patient weighed 50 Kg consisted of boiled rice, 1.200 Gm, eggs, two, potato, 100 Gm, spinach, 100 Gm, cabbage 100 Gm, beef, 100 Gm, miso and soy, equaling 2,110 calories, which contained protein, 86 Gm, fat, 17 Gm, and carbohydrate, 391 Gm

The diet of 30 calories per kilogram given to the same subject consisted of boiled rice, 900 Gm, spinach, 100 Gm, cabbage, 100 Gm, potato, 100 Gm, beef, 40 Gm, miso and soy, equaling 1,520 calories, which contained protein, 54 Gm, fat, 27 Gm, and carbohydrate, 312 Gm

TABLE 4—Data for Subjects Using Different Diets Successively for a Period

Case	Age	Date	Height in Cm	Surface Area		Respi- ration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respi- ratory Quotient	Calories for Each 24 Hours	Calories per Square Meter per Hour (Du Bois)	Basal Metabolic Rate			Diet, Calories per Kg of Body Weight	Days the Same Diet Was Used
				Weight in Kg	Height-Weight Formula, Sq Meters							Du Bois Standards, per Cent	Harris and Benedict Standards, per Cent	Du Bois Standards, per Cent		
1	23	5/17	160.7	56.4	1.59	66	170	200	0.85	1,401	36.8	— 6.9	— 5.8	Usual	40.0	1
		5/18		56.7	1.59	66	182	210	0.86	1,473	38.6	— 2.3	— 1.5	40.0	6	
		5/23		56.7	1.59	66	183	211	0.85	1,481	38.8	— 1.7	— 0.9	40.0	6	
		5/25		56.8	1.59	61	177	204	0.88	1,435	37.6	— 4.8	— 4.1	30.0	2	
		5/28		56.5	1.59	74	165	203	0.76	1,393	36.5	— 7.6	— 6.7	30.0	3	
		5/29		56.4	1.59	76	153	211	0.75	1,442	37.8	— 4.3	— 3.3	30.0	4	
		5/30		56.4	1.59	71	171	204	0.84	1,420	37.2	— 5.8	— 4.7	30.0	4	
2	25	6/25	170.0	56.8	1.66	60	176	180	0.93	1,351	33.9	— 14.1	— 11.6	Usual	40.0	1
		6/26		56.3	1.65	58	163	183	0.89	1,295	32.7	— 17.2	— 14.9	40.0	2	
		6/27		56.3	1.65	54	176	189	0.92	1,338	33.8	— 14.4	— 12.1	40.0	3	
		6/28		56.3	1.65	48	161	179	0.90	1,275	32.2	— 18.5	— 16.2	40.0	1	
		6/29		55.2	1.64	59	178	197	0.91	1,385	35.2	— 10.9	— 8.1	30.0	2	
		6/30		55.3	1.64	56	150	180	0.83	1,256	31.0	— 19.2	— 16.7	30.0	3	
		7/ 1		54.7	1.63	56	174	186	0.94	1,330	34.0	— 13.9	— 11.3	30.0	4	
3	18	7/ 2	151.7	54.7	1.63	55	170	182	0.93	1,303	33.3	— 15.7	— 13.1	30.0	1	
		5/28		48.2	1.42	57	168	203	0.82	1,411	41.4	— 1.0	— 3.1	40.0	2	
		5/29		48.4	1.42	56	176	194	0.91	1,384	40.6	— 1.0	— 1.1	40.0	3	
		5/30		48.6	1.43	56	163	185	0.85	1,311	38.2	— 6.8	— 4.4	40.0	4	
		5/31		49.2	1.43	56	179	192	0.93	1,338	39.0	— 4.9	— 3.0	40.0	1	
		6/ 1		49.2	1.43	54	178	191	0.93	1,369	39.9	— 2.7	— 0.8	30.0	2	
		6/ 2		48.7	1.43	56	171	197	0.87	1,390	40.5	— 1.2	— 1.2	30.0	5	
6	7	6/ 5	48.2	48.4	1.42	56	169	192	0.83	1,353	39.7	— 3.2	— 1.2	30.0	6	
		6/ 7		48.2	1.42	55	162	185	0.90	1,309	38.4	— 6.3	— 4.2	30.0	7	
		6/ 9		48.2	1.42	56	175	189	0.86	1,326	38.9	— 5.1	— 3.0	30.0	8	
		6/ 6		48.1	1.42	59	167	189	0.92	1,346	39.5	— 3.6	— 1.5	30.0	9	

that a heavy meal on the previous day, especially in the evening, causes an increase. We made an investigation as to whether different diets and different amounts of nourishment have any influence on the basal metabolism. Table 3 gives a comparison of the basal metabolism of patients who observed usual dietary habits on the previous day and the same patients given 40 calories per kilogram of body weight per day. Similarly, table 4 gives a comparison of the basal metabolism of a patient on 30 calories and on 40 calories of the usual diet on the previous day. The influence of these moderate changes of diet on the basal metabolism is not significant. Table 5 also shows that a relatively prolonged use of different diets has almost no influence on the basal metabolism when the amount of the diet is not extraordinary.

From the foregoing results, the conclusion is that the basal metabolism of healthy Japanese is quite like that of Americans and Europeans and that no racial difference exists.

Benedict and Roth¹⁷ found no significant difference in the metabolism of vegetarians and nonvegetarians. The food used in Japan is usually much richer in carbohydrate and poorer in fat than the Western style and the cooking also is quite different. In some cases we therefore prescribed Western cooking also on the day previous to the measurement and found no significant change in the basal metabolism. From these facts it is evident that the quality of the food has but little significance in the basal metabolism if enough essential foodstuff is given.

SUMMARY

In metabolism measurements on fifty-three normal Japanese, forty-two men and eleven women, ranging in age from 22 to 28 for the former and from 20 to 22 for the latter, the average height of the men was 161.9 cm and of the women, 150.5 cm. The average weight for the former was 51.85 Kg and for the latter, 50.0 Kg. The average surface area according to the Du Bois height-weight factors was 1.53 square meters, and according to the Harris and Benedict height-weight factors was also 1.53 square meters for the former and 1.43 and 1.47 square meters for the latter.

The vital capacity of the eleven women was somewhat low as compared with American data, being on the average 16.5 cc per centimeter of height and 1.76 liters per square meter of surface area.

The blood pressure of the eleven women was normal.

The average pulse rate for the men was 64 beats per minute, with a minimum of 52 and a maximum of 80, and for women 70, with a minimum of 58 and a maximum of 90, values that are in accordance with American data considering that our subjects were all relatively young.

¹⁷ Benedict, F. G., and Roth, P. *J. Biol. Chem.* **20**: 231, 1915.

The respiration rate varied from 8 to 22 respirations per minute, averaging thirteen for men, for women it was from 8 to 21, averaging 15. When the subjects were breathing normally in the room, without mask, the average rate was 15 and 17, respectively.

The basal metabolism in 96 per cent of the cases showed deviations less than ± 15 per cent, in 87 per cent of the cases less than ± 10 per cent from the Harris and Benedict standards. The average deviation of the actually measured metabolism from the standards is -0.2 per cent for males and -3.9 per cent for females. A comparison of the heat production per square meter of body surface per hour with the Aub and Du Bois standards shows 98 per cent of the whole cases to be within ± 15 per cent, 89 per cent within ± 10 per cent of the standards. The average heat production in the males per square meter per hour was 38.7 calories, -2 per cent, and in the females 36.75 calories, -0.7 per cent of the standard. In view of the fact that Krogh, Benedict and others consider the present standards to be probably 4 or 5 per cent or more too high and that a comparison of the heat production in our cases with the standards of Du Bois as modified by Sanborn showed nearly the same percentage to be within ± 15 per cent of the original standards, it may be concluded that the basal metabolism of healthy Japanese is quite like that of Americans and Europeans and that no racial difference exists. Consequently we may have the convenience of applying the Western standards in the metabolic measurement of our subjects.

THE MECHANISM OF PAIN IN GASTRIC AND DUODENAL ULCERS

I ACHLORHYDRIA¹

WALTER LINCOLN PALMER, M D
CHICAGO

INTRODUCTION

The genesis of pain arising from the stomach and intestine as the result of both functional and organic disorders has attracted much attention in recent years. Inflammation, muscle tension, acid irritation, edema, peritoneal irritation and perineural infiltration have all been ascribed their various rôles. The present work was undertaken with the hope that some aid might be obtained from a clearer understanding of the mechanism of pain in gastric and duodenal ulcers. It has naturally led into other fields at times, but attention has been focused chiefly on the benign peptic ulcer. One of the first problems encountered was that of the occurrence of ulcer and ulcer pain with achlorhydria.

LITERATURE

In the literature many allusions are found to ulcers with achlorhydria, but few of them are definite. For instance, in 1911, Gibson¹ stated that the free acidity in his ulcer cases varied from 0 to 0.18 per cent. Friedenwald,² in 1912, merely noted that hypochlorhydria or anacidity was observed in 188 of his 810 cases, or 23.2 per cent. Smithies³ reported in 1913 that seven of his series of 131 cases had free acidities between 0 and 10. Crispin,⁴ in 1916, reported eleven cases of duodenal ulcer in which the diagnosis was proved at operation, and in which there was achlorhydria. Eusterman⁵ reported a case of gastric ulcer with anacidity in 1921. The following year Moynihan⁶ found achlor-

¹ A dissertation submitted to the faculty of the Ogden Graduate School of Science in candidacy for the degree of doctor of philosophy.

² From the Seymour Coman Fellowship in the Department of Physiology of the University of Chicago and the Cook County Hospital.

¹ Gibson, G. A. Duodenal Ulcer Discussion, *Edinburgh M. J.* **6** 325 (April) 1911.

² Friedenwald, Julius. A Clinical Study of a Thousand Cases of Ulcer of Stomach and Duodenum, *Am. J. M. Sc.* **144** 157, 1912.

³ Smithies, Frank. Gastric Ulcer Without Food Retention, *Am. J. M. Sc.* **145**:340-357, 1913.

⁴ Crispin. Duodenal Ulcer with Achlorhydria, *Interstate M. J.* **23** 890 (March) 1916.

⁵ Eusterman, G. B. Ulcer Syndrome Despite Achlorhydria, *M. Clin. N. Amer.* **5**:40 (Sept.) 1921.

⁶ Moynihan, Berkeley. Some Problems on Gastric and Duodenal Ulcer, *Brit. M. J.* **1** 221 (Feb. 10) 1923.

hydria to be present in five of thirty-nine cases of gastric ulcer, and in four of seventy-one cases of duodenal ulcer. The same year, Bell⁷ reported four cases of achlorhydria in twenty-seven cases of gastric ulcer, 14.8 per cent. In 1924, Heintz and Welker⁸ reported three cases of gastric ulcer without free acidity. Udaonda⁹ in Montevideo reported fifteen such cases in 1925. Eusterman¹⁰ has recently stated that 4.5 per cent of gastric ulcers will show an anacidity. The number of reported cases, then, of peptic ulcer with achlorhydria is large, and its reported frequency in gastric and duodenal ulcers high, ranging from 4.5 to 23 per cent.

The explanation for the varying frequency of this condition in the different clinics is not apparent. There is, of course, the possibility that in some clinics patients with an indefinite abdominal distress are classified incorrectly as patients with ulcer, and also that in other clinics possible ulcers are excluded because of the apparent achlorhydria.

If we are to accept these reported cases, however, as bona fide cases of peptic ulcer with true achlorhydria, we must first examine them critically to determine whether they fulfil the requirements one has a right to expect such a case to fulfil, namely, is there adequate proof, first, that they are really simple benign peptic ulcers and, second, that true achlorhydria is present? The finding of a gastric ulcer at operation or at roentgen-ray examination is not adequate evidence of the character of the lesion, for the possibility of cancer and of syphilis must be excluded. The frequency of anacidity in both of these conditions is well known. Even the failure to find evidence of carcinoma microscopically is not incontrovertible evidence of the benign nature of the lesion, for Moynihan⁶ has reported two such cases in which the patients died from carcinoma metastases three and five years later. The finding of a definite duodenal ulcer at operation, however, as Crispin reported must be considered as more adequate evidence of ulcer.

But what are we to consider as adequate evidence of achlorhydria? It is not the intent of this article to enter into a detailed discussion of the mechanism of gastric secretion. This has been well worked out by Ivy, Lim and McCarthy¹¹. Dobson¹² has grouped the achlorhydrias

7 Bell, J. R. Gastric Ulcer and Achlorhydria, *Arch Int Med* **32** 663 (Nov.) 1923

8 Heintz, E. L., and Welker, W. H. Acidity Curves in Gastric, Duodenal and Mixed Ulcers, *Ann Clin Med* **3** 371 (Nov.) 1924

9 Udaonda. Functional Achylia, *An de Fac de med*, Montevideo, **9** 799 (Sept.) 1924

10 Eusterman. The Newer Aspects of Gastric Carcinoma, *Radiology* **6** 409-415 (May) 1926

11 Ivy, A. C., Lim, R. K., and McCarthy, J. E. Contributions to the Physiology of Gastric Secretion, *Quart J Exper Physiol* **15** 13-68 (March) 1925

12 Dobson, H. V. Effect of Histamine on Gastric Secretion, *J A M A* **84** 158 (Jan. 17) 1925

on the basis of their response to histamine. The question at present is to determine the reliability of the clinical tests that are generally considered as adequate evidence of achlorhydria.

With a single exception, which will be mentioned later, all the cases cited in the literature as instances of ulcer with achlorhydria are based on the failure to find free acid either in an ordinary Ewald test meal or Boas test meal removed at the end of an hour, or in a fractional Ewald or Boas test meal in which samples are removed and titrated every fifteen minutes. The first table shows an illustration of the fallacy involved in assuming that anacidity in an Ewald test meal is adequate evidence of true achlorhydria. This is a list of eighteen persons having either a proved or a probable peptic ulcer, who had an absence of free acid in one Ewald test meal but free acid at another

TABLE 1—*Cases Illustrating Wide Variations in Gastric Acidities as Revealed by Ewald Test Meals*

Case	Free Acidity *	Total Acidity
1	0-5	52-23
2	0-7	17-20
3	0-24	40-60
4	0-29 †	34-68 †
5	0-25	25-68
6	0-28	25-35
7	0-45-80	20-60-92
8	0-43-45	11-60-54
9	0-15-18	30-50-42
10	0-15-18-59	8-35-37-83
11	0-10-43-45	42-29-48-60
12	0- 8-16-18-20-48	14-22-36-48-48-70
13	0-trace-11-19-35	20-30-39-41-80
14	0-0-11	28-34-21
15	0-0-25	52-78-79
16	0-0-14-70	35-43-50-88
17	0-0-24-40-40	8-13-70-54-63

* The free acid values were arbitrarily arranged to increase from left to right

† Control aspiration

time. These eighteen were selected from a series of 1,469 cases recently reviewed at the Presbyterian Hospital. Four of them showed no free acid in two Ewald test meals. Furthermore, the total acidity in four was less than 15. This is of interest because Kelling,¹³ Schutz¹⁴ and Girardi¹⁵ have stated that a total acidity of less than 15 or 20 may be considered as evidence of complete achlorhydria. Attention is also called to the wide range in the free acidity values, from 0 to 70.

The second table shows the fallacy involved in assuming that anacidity as revealed by a fractional test meal is adequate evidence of

13 Kelling, G. Statistisches über den Salzsauremangel im Magen, Arch f Verdauungskr **15** 568, 1909

14 Schutz, E. "Über Anacidität," Arch f Verdauungskr **30** 233 (Jan) 1921

15 Girardi. False Achylia Gastrica, Gazz d osp **4** 412, 1924

achlorhydria Here again it is noted that the maximum total acidity in two cases is less than 15 and in another case is less than 20

Hence, the reported cases of peptic ulcer with achlorhydria have to be considered as unproved because the evidence presented of true and complete achlorhydria is inadequate

TABLE 2—*Cases Illustrating Wide Variations in Gastric Acidities as Revealed by Fractional and Ewald Test Meals**

	Fractional Meal Maximum Acidity		Ewald Meal	
	Free	Total	Free	Total
Chronic ulcer of body of stomach Page 106, case 6	0	17	41	70
case 100	0	33	28	44
Hour-glass stomach Page 109, case 242	0	26	38	52
Visceroptosis Page 109, case 200	0	6	19	36
Carcinoma of stomach Page 119, case 180	0	53	32	57
Cirrhosis of the liver Page 130, case 195	0	12	29	49

* These cases are taken from Donald Hunter's "Study of Fractional Test Meal," Quart J Med 16 95-134 (Jan) 1923

INVESTIGATIONS AT THE PRESBYTERIAN HOSPITAL

In an effort to find more conclusive data on the subject, the files at the Presbyterian Hospital were searched for such cases recently, with the thought that perhaps it might be possible to find there proved cases of peptic ulcer in which repeated gastric analyses had failed to show free acid at any time The Presbyterian Hospital was chosen because at no other hospital, so far as I know, has there been such

TABLE 3—*Cases of Proved or Probable Peptic Ulcer Showing No Evidence of Free Hydrochloric Acid (Presbyterian Hospital Series)*

Case	Ewald Acidities	
	Free	Total
1	0	32
2	0	16
3	0	12
4	0 *	23 *
5	0-0-0 †	8-12-62 †
6	0-0 ‡	110-20 †
7	0-0-0-0	10-18-20-28

* Motor meal

† Riegel meal

‡ Fractional meal, Mayo Clinic

extensive use of Sippy's therapeutic aspiration, which is the aspiration made at the height of distress and which will give, on the average, a higher acid value than the Ewald test meal The study included 1,004 proved ulcers and 465 probable ulcers The third table shows a list of all of the cases found which failed to show free acid at any time The first four may be discarded at once because the sole evidence of achlorhydria is that of a single test meal The fifth case may be disregarded

for three reasons first, because a definite diagnosis of ulcer was not made and the symptoms were not typical ulcer symptoms but consisted chiefly of morning nausea and loss of appetite, second, because there was no definite evidence of ulcer, and, third, because the patient had previously had a gastro-enterostomy and a gastric resection which altered the gastric chemistry. It is known that an "excessive amount of free hydrochloric acid" was present prior to the third operation.¹⁶ The sixth and seventh cases cannot be excluded so easily, and it is necessary to consider them in detail.

A brief resumé of the sixth case is as follows

L J P, a man, aged 53, on Oct 8, 1914, entered the Presbyterian Hospital, in the service of Dr B W Sippy, complaining of epigastric distress of seventeen years' duration—a fair ulcer story until the last year or two. The Ewald meal was 0-10. The motor meal was 0-14.

On October 9, a therapeutic aspiration was performed for distress. Free hydrochloric acid was 0, total, 70.

On October 12, a motor meal test was 0-185, long bacilli and lactic acid were present. Sixteen other aspirations at various intervals after eating during the following week failed to reveal free hydrochloric acid at any time, making twenty aspirations in all without free acid.

On October 19, a laparotomy was performed by Dr Dean Lewis. "The stomach wall was found edematous with a ring-shaped thickening of soft consistency about the pylorus." The diagnosis was syphilis of the stomach with obstruction. A posterior gastro-enterostomy was done.

On November 3, the diagnosis at discharge was pyloric obstruction and ulcer of the stomach.

In August, 1920, he consulted the Mayo Clinic for stomach trouble. A fractional test meal showed a maximum free acidity of 0, total acidity, 20. Roentgen-ray examination revealed an extensive lesion of the stomach, gastro-enterostomy free. The stomach was reported to be unusually small and shrunken. A blood Wassermann test was strongly positive, a spinal fluid test was negative. There was a history of a primary syphilitic lesion in 1895. The diagnosis was posterior sclerosis, probably arteriosclerosis, and gastric syphilis.

In August, 1921, the patient died. The diagnosis was arteriosclerosis, cerebral type, and syphilis of the stomach. No necropsy was performed.

In spite of the rarity of gastric syphilis, apparently there is sufficient evidence to justify this diagnosis, and hence it must be excluded.

A brief resumé of the seventh case follows

O F, a man, aged 56, on Dec 4, 1913, entered the Presbyterian Hospital, in the service of Dr Dean Lewis, complaining of constipation and epigastric pain of a year's duration, the distress was definitely not typical ulcer distress.

On December 5, an Ewald test meal showed free hydrochloric acid, 0, total hydrochloric acid, 28. A motor meal showed free hydrochloric acid, 0.

On December 6, an Ewald test meal showed free hydrochloric acid, 0, total, 20. A motor meal showed free hydrochloric acid, 0.

On December 9, a therapeutic aspiration of 60 cc was performed for distress. Free hydrochloric acid was 0, total, 33. No relief was felt.

On December 12, a laparotomy was performed by Dr Lewis. There was an old scar from a healed gastric ulcer near the pylorus and a duodenal ulcer with a definite crater. There was no evidence of malignancy. A gastro-enterostomy was done.

On December 27, an Ewald test meal showed free hydrochloric acid, 0, total, 10, lactic, 0, a motor meal, free, 0, total, 10.

16 Davis, T I. Personal communication to the author.

On December 29, an Ewald test meal showed free hydrochloric acid, 0, total, 18

On January 17, a therapeutic aspiration of 200 cc was performed for severe distress. Free hydrochloric acid was 0, total, 17. No relief was felt.

On February 14, the patient committed suicide because of failure to obtain relief from distress. Necropsy revealed a healed duodenal ulcer. Sections through the base of the scar revealed no evidence of malignancy.

Several points are of great interest. The diagnosis of duodenal ulcer was proved by laparotomy and by the finding of the scar of the healed ulcer at necropsy. No free acid was present in any one of the nine gastric analyses. Perhaps this cannot be considered as true and complete achlorhydria because the total acidity was twice more than 15 and once more than 20, and there is no record of a histamine test. Nevertheless, it must be considered as a practical achlorhydria. Certainly there is more evidence of achlorhydria here than is reported to have been present in any of the cases cited in the literature. But there is another important thing to be noted here—the man committed suicide because of failure to obtain relief from a distress which continued after the ulcer had healed. In other words, the only distress of which he complained, the distress for which he entered the hospital and underwent an operation, continued unrelieved after the ulcer had healed, and was severe enough to cause him to commit suicide. No explanation for the distress was found at necropsy.

Probably this case should be accepted as one of duodenal ulcer without free hydrochloric acid. However, if we are to accept it as a case of ulcer distress without free acid, we must take the stand that a healed ulcer can cause pain. Dr. Eusterman of the Mayo Clinic has called my attention recently to a case of theirs in which typical ulcer pain was present, but in which at necropsy a healed duodenal ulcer was the only lesion found. Eusterman¹⁷ also states that patients with pyloroplasties will often have a recurrence of ulcer symptoms without an ulcer being demonstrable at reoperation. Clinical experience on the whole, however, teaches that painful ulcers are active ulcers, and that healed ulcers are painless. At present, this seems to be the most rational view, and hence one hesitates to conclude that the distress in this particular case was in any way related to the ulcer, either before it healed or after it healed. At the same time, it must be admitted that the question is an open one and calls for further investigation.

Hence of this series of 1,004 proved ulcers and 465 probable ulcers, as is shown in table 4, all four of the probable or suspected ulcers with achlorhydria must be disregarded because of the lack of evidence both as regards the presence of ulcer and the presence of achlorhydria, one fairly well proved duodenal ulcer must be disregarded because of the

¹⁷ Eusterman, G. B. Personal communication to the author from the Mayo Clinic.

lack of sufficient evidence as regards the achlorhydria, one gastric ulcer must be reclassified as a probable syphilitic lesion, and one duodenal ulcer must be accepted as a case of duodenal ulcer without free acid and apparently without pain directly attributable to the ulcer. In other words, there is no incidence of achlorhydria in the proved gastric ulcers, and of only 0.12 per cent in the proved duodenal ulcers—the one case

INVESTIGATIONS AT THE MAYO CLINIC

Because of the marked difference between these observations and those in the literature, it seemed wise to see what definite evidence could be obtained on the subject at the Mayo Clinic. Bueerman¹⁸ has been reviewing their records recently and is preparing a report. In his notes, which he allowed me to see, three cases particularly are of interest. The first patient was a person with roentgenologic evidence of duodenal ulcer. Three fractional test meals revealed an entire absence of free acid and a total of not over 20, but a free acid of 14 was obtained in

TABLE 4—*Summary of Cases Reviewed at Presbyterian Hospital*

	Proved Ulcers			Probable Ulcers
	Gastric	Duodenal	Total	
Number of cases	110	894	1,004	465
Free acid present	109	892	1,001	461
Possible achlorhydrias	1	2	3	4
Syphilis	1		1	
Inadequate evidence of achlorhydria		1	1	4
Ulcer with achlorhydria	0	1	1	0
Incidence		0.12%	0.1%	

response to the subcutaneous injection of a quarter of a milligram of histamine hydrochloride. This shows the fallacy of accepting even three fractional test meals as conclusive evidence of complete achlorhydria. The second is a patient with a good ulcer history of ten years' duration and roentgenologic evidence of a duodenal lesion. Two fractional test meals revealed an absence of free acid and total acidities of 26 and 30. The subcutaneous injection of 0.5 mg. of histamine chloride failed to produce any free acid, but a total acidity of 40 was noted. Aspiration is said to have been performed in this case at the time of distress without the finding of free acid, but the figures as regards the amount of gastric content obtained and its total acidity are not available. This must be regarded as a suggestive case, but one hesitates to accept it as conclusive until the figures are recorded and its further course is followed. The third case is one with a rather typical ulcer history of ten months' duration. A penetrating duodenal ulcer was found at operation, and the symptoms did not reappear after gastro-enterostomy.

18 Bueerman, W. H. Personal communication to the author. The Surgical Significance of Duodenal Ulcer with Achlorhydria, to be published.

Two fractional test meals before gastro-enterostomy and four at various times later failed to reveal any evidence of free acid. A year later, the patient returned with a well developed pernicious anemia. An examination of the gastric content at the time of distress was not made. This is, perhaps, a better case than the preceding one, but one hesitates to accept it also without knowing more of the details, such as the time of the appearance of the pernicious anemia and the character of the gastric content at the time of distress.

Of these three cases, then, the first was shown not to be a true achlorhydria by means of the histamine test, the other two are very suggestive and must be considered as cases of duodenal ulcer with possibly complete achlorhydria.

ADDITIONAL CASES

There has recently been a patient at the Cook County Hospital who must be considered in this connection.

M. F., a man, aged 56, in September 1923, consulted the Pelton Clinic,¹⁹ Elgin, Ill., for "gnawing, burning" epigastric distress of four or five years' duration, it was worse in the winter and practically absent in the summer, coming on one-half to three hours after eating and lasting continuously for an hour or two, when it would disappear spontaneously or be relieved by eating or by vomiting. A drachm (4 Gm.) of soda gave relief for only half an hour or so. An Ewald test meal showed free acid, 0, total, 11. Boas-Opler bacilli were absent. Milk coagulation was negative in all the tubes. A laparotomy revealed a diseased gallbladder with extensive adhesions and an old ulcer scar on the anterior surface of the duodenum. A cholecystectomy and a posterior gastro-enterostomy were done.

On Dec. 2, 1925, the patient entered Cook County Hospital, complaining of severe, cramplike pain about the navel, different from his old pain, and of the vomiting of a quart of blood twelve hours previously. A therapeutic aspiration of 11 cc for severe pain was performed. Free acid was 0, total, 39. No relief was obtained from the aspiration. The distress subsided forty-eight hours later.

On December 3, an Ewald test meal revealed free acid, 0, total, 40. Blood was present. A motor meal showed free acid, 0, total, 36. Blood was present.

On Feb. 2, 1926, an Ewald test meal showed free acid was 0, total, 18.

On February 19, 1 mg. of histamine hydrochloride was given subcutaneously. Free acid was 0, total, 11.

On April 7, 15 mg. of histamine hydrochloride was given subcutaneously. Free acid was 0, total, 14.

This case must also be considered as suggestive, but it cannot be accepted as conclusive, because the evidence of true achlorhydria prior to the gastro-enterostomy is inadequate, and the nature of the lesion following gastro-enterostomy was not conclusively determined.

There seems to be reported in the literature only one case of ulcer with no free acid in a therapeutic aspiration at the time of distress. This is reported separately by Eusterman⁵ and by Hardt²⁰. Adequate free

¹⁹ Pelton, O. L., Jr. Personal communication to the author from the Pelton Clinic, Elgin, Ill.

²⁰ Hardt, L. L. J. Studies of the Cause of Pain in Gastric and Duodenal Ulcers. II. Peristalsis as Direct Cause of Pain in Gastric Ulcers with Achylia and in Duodenal Ulcers, Arch. Int. Med. 29: 684 (May) 1922.

acidity was present in this case prior to gastro-enterostomy for a duodenal ulcer. Later, the patient returned with a large penetrating gastric ulcer. At this time, according to Eusterman, aspirations made during his pain averaged a total acidity of 6, no free acid, and an average amount of 50 cc, consisting almost entirely of a bile tinged fluid and some mucus.

Ryle²¹ reports another case of recurrence after gastro-enterostomy in which pain is said to have occurred in the absence of free acidity. There is no mention of therapeutic aspirations made at the time of distress, and one must infer that the statement is based on test meal observations only.

CONCLUSIONS

It is difficult to draw many definite conclusions on this subject at present, but one may summarize the situation as follows:

- 1 Repeated Ewald or fractional test meals cannot be accepted as giving conclusive evidence of achlorhydria even when the total acidity is less than 15.

- 2 The previously reported cases of duodenal or gastric ulcer with achlorhydria cannot be accepted as being satisfactorily proved as yet.

- 3 In a case of duodenal ulcer with no free acid in nine Ewald test meals, motor meals and therapeutic aspirations reported, there is evidence that the pain cannot be attributed to the ulcer with certainty, for it continued after the ulcer had healed. This is the only case of definite achlorhydria found in a review of 1,004 proved gastric and duodenal ulcers at the Presbyterian Hospital.

- 4 An absence of free acid both in test meals and in therapeutic aspirations made at the time of distress attributable to a benign gastric or duodenal ulcer has been reported definitely in only one case, that of a perforated gastric ulcer.

- 5 Because of the practical importance of this question in the genesis, chronicity and pain of ulcer, it is hoped that all those who are in a position to manage and observe patients with ulcer will prove any achylia which they may encounter in proved ulcers by repeated test meals, by injections of histamine and by repeated therapeutic aspirations and titrations made at the time of distress attributable to the ulcer.

²¹ Ryle, J. A. *Gastric Function in Health and Disease*, London, Oxford Univ. Press, 1926, p. 64.

RENAL DWARFISM

REPORT OF A CASE *

FREDERIC W LATHROP, M D

BALTIMORE

The association of chronic nephritis with bone changes in adolescents is apparently so uncommon as to have escaped general attention. In 1883, Lucas¹ reported several cases of late rickets associated with albuminuria. Among these was one case of chronic nephritis associated with rachitic changes in the bones. The case was, however, not fully studied or followed. Apparently he did not recognize the case as peculiarly one of chronic nephritis in which rickets occurred. In 1911-1912, Fletcher, Miller and Parsons² described instances of the association of chronic interstitial nephritis with bone changes, but it was not until 1920 that Barber compiled a series of ten cases in adolescents and called the syndrome "renal dwarfism."³ This aroused considerable discussion in the British literature, but until recently the condition has failed to attract any appreciable notice in the American journals.⁴

This disease as described by the British authors is characterized by an insidious onset in early puberty of mild headache, drowsiness, albuminuria, fixation of the specific gravity of the urine at a low level, polyuria, anemia, dwarfism unassociated with any mental changes, bone deformities of a rachitic nature, failure of development of the secondary sexual characteristics, slight cardiovascular change, and inevitable termination in uremia sometime in the second decade of life. The symptoms are thus largely those of chronic nephritis, plus bone changes simulating rickets.

Only seven cases that were examined at necropsy have been recorded in the literature.⁵ The pathologic picture they have presented is fairly characteristic. As a rule the cardiovascular system is normal. The kidneys show a chronic interstitial nephritis. The bones have apparently

* From the medical clinic, Johns Hopkins University Medical Department

1 Lucas, R. C. *Lancet*, 1883, pp 79, 993

2 Fletcher, H. M. *Proc Roy Soc Med (Sect Dis Child)* **4** 95, 1911
Miller, R. *Proc Roy Soc Med (Sect Dis Child)* **5** 38, 1911. Parsons, L.
Brit M J **2** 481, 1911. Miller, R., and Parsons, L. *Brit J Child Dis* **9** 289,
1912

3 Barber, Hugh. *Brit M J* **2** 1204, 1913, *Quart J Med* **14** 205, 1920,
Lancet **1** 18 (Jan 3) 1920, *Guy's Hosp Rep* **71** 62 (Jan) 1922

4 Shipley, P. G., Park, E. A., McCollum, E. V., and Simmonds, N. *Am J Dis Child* **23** 91 (Feb) 1922. Smith and Walsh. To be published

5 Barber (footnote 3). Paterson, D. H. *Proc Roy Soc Med (Sect Dis Child)* **13** 107 (June) 1920. *Brit J Child Dis* **18** 186 (Oct-Dec) 1921.
Lancet **1** 944 (May 13) 1922. Naish, A. E. *Brit J Child Dis* **9** 337, 1912

not been studied by the pathologists except by Patterson,⁶ who, however, differentiates the changes that occur from those of rickets and considers the changes as due to some undetermined fault in the calcium metabolism

The condition is apparently relatively uncommon. In the fourteen cases so far reported,⁷ the age of onset varied from 7 to 17 years, with an average age at onset of 12½ years. The age at death varied from 9½ to 20, with an average of 14 years. The average duration of symptoms was a trifle over one and one-half years, varying from six months to six years. Barber in his series³ gives two cases of chronic interstitial nephritis in which infantilism was present without bone deformities. There is an allied group of cases in which the symptoms of nephritis and the bone changes were present at birth or shortly after.⁸ All the latter patients died before the age of 10.

The following case of renal dwarfism is of interest not only because it offers such a typical example of renal dwarfism but also because it gave us the opportunity to make certain chemical studies of the patient's blood over a long period of time.

REPORT OF CASE

E. C., a girl, aged 15, was admitted to the Johns Hopkins Hospital, April 6, 1925, complaining of drowsiness and anorexia. The patient was the youngest of ten children, all of whom were living and well. There was no history of tuberculosis, syphilis or renal disease in the family. All the other members of the family were fairly tall. The patient had pertussis at 8 months, smallpox at 5 years, measles at 8 years, influenza at 9, typhoid fever at 11, and mumps at 13. There was no history to suggest scarlatina, diphtheria or tonsillitis. She was never strong but seemed to develop normally till after the attack of typhoid fever at 11, since then a distinct retardation of physical growth had been noticed. Mentally the child had continued to develop normally, and was unusually bright in school. Her catamenia had not yet begun.

The onset of the present illness was dated definitely from the age of 12, two and one-half years before admission. At that time there had been a gradual onset of fatigability, lack of energy and drowsiness. She became so drowsy she would fall asleep while eating. She was taken to a physician because her parents believed she might be having sleeping sickness. It is reported that albumin was found in the urine at that time. In November, 1922, she was admitted to the Montgomery General Hospital, Montgomery, W. Va. The urine at that time showed a light cloud of albumin, an average specific gravity of 1.006, and an occasional granular cast. The blood pressure was 110 systolic, 70 diastolic. The phthalein output was 11 per cent and the nonprotein nitrogen 74 mg. (table 1). She was in the hospital seven weeks and was discharged improved. During the succeeding two and one-half years she had been in and out of the Montgomery Hospital five times. Soon after the first discharge her drowsiness returned, and

6 Patterson (footnote 5, second reference)

7 Fletcher, Miller, Parsons, Miller and Parsons (footnote 2). Barber (footnote 3). Patterson (footnote 5, second reference). Naish (footnote 5, fifth reference). Feiling, A., and Holyoak, W. L. *Proc. Roy. Soc. Med. (Clin. Sect.)* 15:1, 1922.

8 Fletcher (footnote 2, first reference). Patterson (footnote 5, second reference).

with it frontal headaches, nausea and vomiting. From this time on her height and weight apparently remained almost stationary. Two years before admission to the Johns Hopkins Hospital there is said to have been a sudden onset of knock-knee, which had become progressively worse but had not interfered with walking. For a year and a half she had had palpitation and dyspnea on exertion, with puffiness of the eyelids in the morning and slight swelling of the feet and ankles at night. For over a year she had had almost constant thirst with polyuria and nycturia. For a month previous to admission to this hospital she had had complete anorexia, with dull pain in the right upper quadrant following meals.

On physical examination, the temperature was 99, the pulse 100, the respirations 20. The height was 4 feet 7½ inches. The weight was 73¾ pounds (33.2 Kg). The blood pressure was 110 systolic, 60 diastolic. The patient was a very

TABLE 1—*Blood Examination at Montgomery General Hospital **

	Nov, 1922	Feb., 1924	March 4, 1924	March 10, 1924	March 14, 1924	March 19, 1924	Jan 26, 1925
Nonprotein nitrogen	74	98	110	118	72	120	161
Urea nitrogen	52	72.6	82	93.3	58	96	
Creatinine		2.5		4.54	3.67	3.14	

* All figures in the tables are in terms of milligrams per hundred cubic centimeters of whole blood. The figures in this table were lent by W. J. Laird, Jr., M.D., Montgomery, W. Va.

TABLE 2—*Blood Examination at Johns Hopkins Hospital*

	April 7, 1925	April 11, 1925	April 13, 1925	April 17, 1925	April 23, 1925	April 30, 1925	May 9, 1925	May 11, 1925	May 13, 1925
Nonprotein nitrogen	100	95.3			113.2	141	176		244
Nonprotein nitrogen of plasma				158					
Creatinine	7.3								
Uric acid	5.3								
Carbon dioxide capacity	30.5			33.2	32.6		21	18.9	21.2
Hydrogen ion concentration of blood							7.32	6.98	
Phosphates			9.2			9.1			9.5
Total calcium			5.9			4.6			4.6
Free calcium						3.8			
Total protein				7.32					
Albumin				4.36					
Globulin (including fibrin)				2.96					
Fibrinogen				0.562					
Albumin globulin ratio				60/40					
Sodium chloride				593					
Sodium									0.290
Sugar					0.099				

intelligent and cooperative child, but rather drowsy. She was well nourished but greatly underdeveloped. The breasts were small, and there was an absence of secondary sexual characteristics. There was a puffiness about the eyes and a pasty pallor to the face. There was a uriferous odor to the breath. The skin was coarse and dry, there was no edema. There was marked genu valgum (fig 1), beading of the costochondral junctions, and a very slight thickening of the epiphyses at the wrists. The ophthalmologic examination showed a normal fundus. The heart was not enlarged to percussion, measuring 7 cm. to the left of the mid-sternal line in the fourth interspace and 4 cm. to the right in the third interspace. No endocardial murmurs were heard. The abdomen was entirely negative, the liver, spleen and kidneys were not felt. The blood showed a red cell count of 2,500,000, hemoglobin, 41 per cent, white cell count, 12,400. The differential count was normal. The urine was pale and clear, with a specific gravity varying

from 1 005 to 1 010 and albumin varying from 1 to 2 Gm per liter (Esbach). Twenty microscopic examinations showed large numbers of leukocytes but no red cells and no casts. The guaiac test was negative in all specimens examined. The figures on certain of the chemical constituents of the blood are given in table 2. Specimens of urine collected at two hour intervals showed a fixation of the specific gravity at from 1 008 to 1 009. The Wassermann reaction was negative. The roentgen ray showed the heart to be normal in size, and showed a marked retarda-

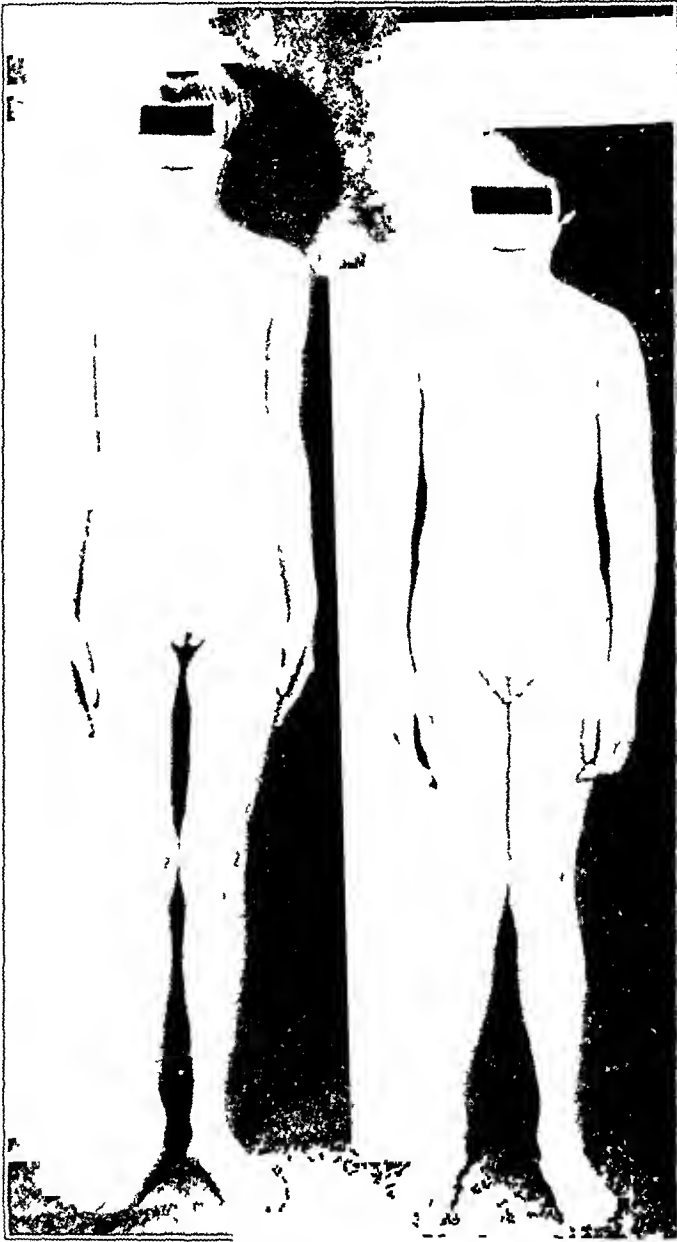


Fig 1—Left, twelve year old diabetic girl, right, patient described here.

tion of development of the epiphyses, especially at the wrist (fig 2). The electrocardiographic report was normal except that the P-R interval was a little long for the age. The blood pressure remained fairly constantly at 120 systolic, 80 diastolic, until the last few days of life, when it became very irregular, ranging from 90 systolic, 20 diastolic, to 150 systolic, 80 diastolic, in a single day. The temperature remained normal except for a terminal rise due to a terminal bronchopneumonia. The pulse remained constantly between 90 and 100.

Her course in the hospital was progressively downward. For the first few weeks she seemed to improve. She became lively and vivacious, playing freely with the girl in the next bed. Contrary to the clinical improvement, however, the nonprotein nitrogen of the blood remained in the neighborhood of 100 mg. She suffered from occasional nausea and on rare occasions she vomited. For one period she complained of transient diplopia. She developed a peculiar brownish pigmentation of the face. May 7, she began to show a drowsiness from which at times it was difficult to arouse her. By the next day it was noticed that she was becoming more dyspneic. She sank rapidly and a few days later was in coma with great air hunger. Alkalis were administered freely, which seemed to lessen slightly the coma and made the breathing much less labored. There was slight



Fig 2—Wrists of patient

bleeding from the nose and mouth. The pulse became irregular and the respirations feeble. The evening of May 14, 1925, she died, apparently of respiratory failure.

Necropsy was performed by Dr. A. R. Rich. The anatomic diagnosis was renal dwarfism, peculiar nephritis, thickening of the bladder mucosa and kidney pelvis, early lobular pneumonia, hyperplastic bone marrow, diphtheric laryngitis and rickets.

Briefly the pathologic report was as follows:

Grossly the heart and blood vessels showed nothing abnormal, but there was diffuse, very fine scarring of the myocardium on microscopic examination.

The bony and renal changes were the most striking. Grossly the bones showed an irregular line of ossification with small yellowish opacities beneath this line. The bone was apparently softer than normal because it was cut more easily than is usual. On microscopic examination, the line of ossification in the ribs was found

to be very irregular and in places between the cartilage and the bone there were broad zones of loose connective tissue in which islands of osteoid tissue were embedded

The kidneys were extraordinary in appearance. They were both distorted pieces of tissue which externally hardly resembled kidneys. The left kidney weighed 40 and the right only 35 Gm. The capsules stripped with difficulty. The surfaces of the kidneys were rough and scarred. On section the kidney architecture was found to be almost unrecognizable. The cortex was only 3 mm in thickness. The organs were very dense and firm and were cut with much more



Fig 3—Left kidney, showing scarring, obliteration of cortex, and A, nodule of compensatory hypertrophy, actual size, with centimeter rule

difficulty than normal kidneys. There were no hemorrhages to be seen in the kidney structure. The blood vessels were prominent but not especially sclerotic. The ureteral lining near the pelvis was distinctly thickened but no fresh inflammatory reaction was seen in the pelvis or ureter. The bladder wall was not thickened but the bladder lining presented a peculiar appearance. It showed no injection of the blood vessels nor any sign of recent inflammation but it was thickened and thrown into translucent whitish plaques having narrow crevices

between them. The plaques were wrinkled. The ureteral orifices were patent. Microscopically the kidneys showed the following picture. A cross section of the entire kidney fitted easily beneath the usual oblong cover slip. There was a complete distortion of the normal kidney architecture. There were numerous old scars throughout the section in which the remnants of tubules and partly or completely obliterated glomeruli and blood vessels were embedded. In these areas collections of small lymphocytes were prominent and the arterioles were numerous because of their being brought together by collapse of the intervening parenchyma. The scars contained many dilated capillaries and venules and in some places there were cavernous telangiectatic dilatations of the capillaries. In

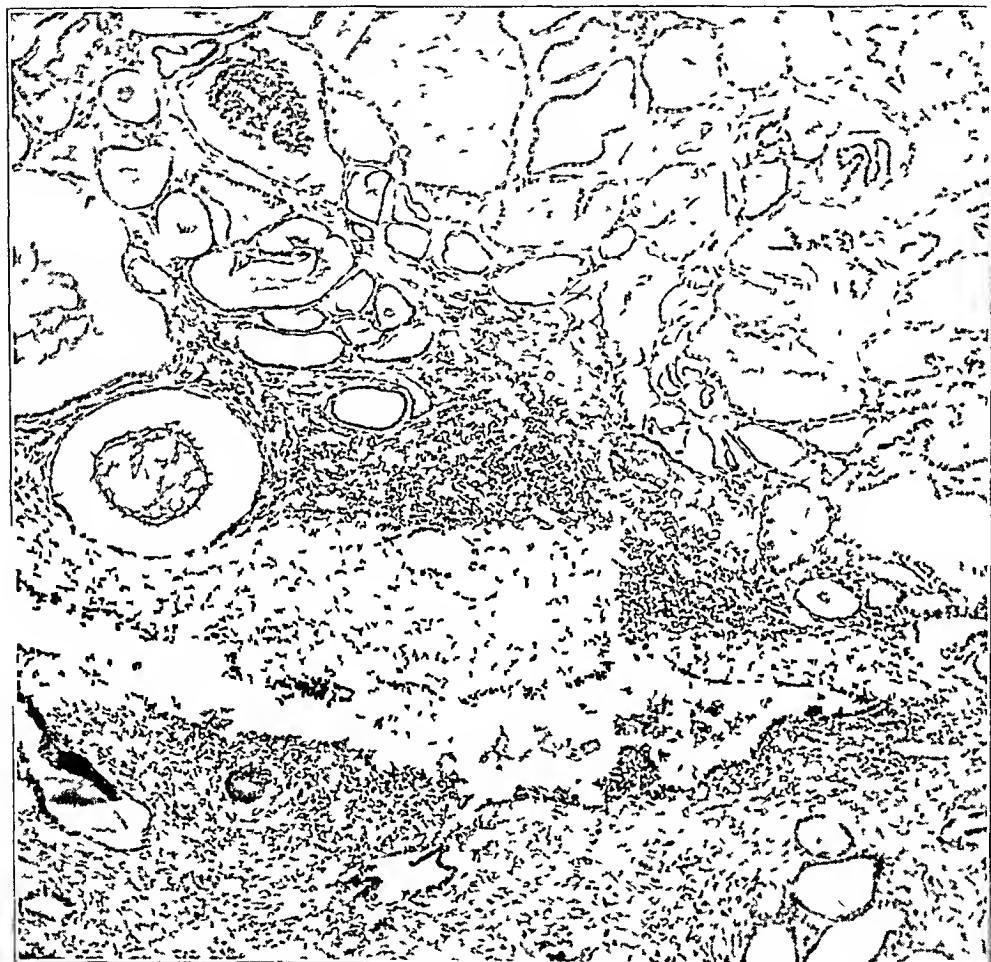


Fig. 4—Pelvis of kidney with round cell infiltration

the regions between these scars there were everywhere enormously dilated tubules lined with low cuboidal cells or, often, quite flattened remains of the epithelial cells. These tubules contained albumin and occasional casts. A few of these tubules were plugged with masses of cellular debris. Other tubules contained a few leukocytes and many red cells. Epithelial cells that were dead were found lining the tubules only occasionally. In several places between the tubules there were rather extraordinary accumulations of large, pale, mononuclear lipid containing cells resembling exactly the lipid laden phagocytes seen in xanthoma or occasionally at the site of chronic inflammation where widespread necrosis of tissue has occurred. Most of the glomeruli among the dilated tubules were normal in

appearance but occasionally partly hyalinized glomeruli and adhesions between the tuft and Bowman's capsule were seen. There were infiltrations of mononuclear wandering cells of all sorts beneath the epithelium of the pelvis (figs 3, 4 and 5).

The liver, lungs, parathyroids, suprarenals and other organs showed no striking pathologic changes.

COMMENT

This disease is very uncommon. Its pathogenesis is little understood. There is no evidence that syphilis or any of the acute illnesses that are known to cause nephritis, such as scarlatina, diphtheria or tonsillitis,



Fig 5—Scarring of kidney

play any rôle in the production of the disease. There is absence of hypertension, cardiac hypertrophy or vascular sclerosis. This would clearly differentiate this type of nephritis from that described by Greene⁹. As more cases come to be reported, however, this distinction may prove to be purely an arbitrary one. In our case the picture is somewhat confused by a chronic infection of the entire genito-urinary

⁹ Greene, C. H. *Am J Dis Child* 23:183 (March) 1922.

tract It would suggest in some respects a chronic cystitis and chronic pyelitis with pyelonephritis and destruction of the kidney parenchyma as secondary effects It is, however, impossible to say which was primarily responsible for the loss of renal substance It might be either a chronic interstitial nephritis with secondary infection of the renal tract or an ascending infection of the renal tract with secondary invasion of the kidney

In most of the cases reported, the lesion is that of chronic interstitial nephritis In our case there was found an extreme reduction of kidney substance, with some areas resembling chronic nephritis but associated with chronic pyelitis and chronic cystitis The end-result, however, is identical—an almost total destruction of the kidney parenchyma with very little disease of the blood vessels

In the patient described here all the characteristic symptoms as given in previously reported cases were present, i e., the insidious onset in the second decade, the nausea and occasional vomiting, frontal headaches, dwarfish, knock-knee, polydipsia, polyuria and nycturia, with anorexia and hunger and uremic coma as the terminal events The physical examination also was similar, showing as it did dwarfism, absence of secondary sexual characteristics, normal blood pressure and normal sized heart, genu valgum, rosary and thickening of the epiphyses, a urine of low specific gravity and albumin with very few casts, a low phthalein excretion, and increased nonprotein nitrogen of the blood

It is unfortunate that the British authors have been unable to furnish any figures as to the chemical constituents of the blood that we might use for comparison We were privileged to obtain studies of certain of the chemical constituents of the blood in the case reported here over quite an extended period (table 2) Two and one-half years before death the nonprotein nitrogen was 74 mg per hundred cubic centimeters, and for more than a year repeated observations showed that it was constantly in the neighborhood of 100 mg The creatinine also was surprisingly high over a long period The calcium and phosphorus figures are particularly interesting and show a complete reversal of the normal values The calcium was in the neighborhood of 5 mg instead of the normal of about 10, and the phosphorus was over 9 mg, the normal being between 4 and 5 The acidosis with a carbon dioxide capacity of 30 per cent by volume is of note in the absence of any hyperpnea or other untoward symptoms It is interesting that in a case of such severe renal insufficiency with maximal nitrogen retention over a long period, at no time except in the terminal stage was there any degree of hypertension

One of the peculiar problems that this case presented was the absence of tetany in spite of a blood calcium of less than 5 mg At no stage was there the slightest clinical evidence of tetany, though on

frequent occasions attempts were made to elicit Chvostek's and Trousseau's signs. Pincus¹⁰ has shown that cases of chronic nephritis with a low blood calcium are free from convulsions if the free calcium is about normal. In this case, although the total calcium was very low, we found the free calcium to be 3.8 mg, which is entirely normal and above the level at which tetany occurs. It is an interesting speculation that the severe acidosis in this patient may have been a factor in keeping the greater part of the calcium in the circulating blood in the ionized form, and thus may have been a factor in preventing the onset of tetany. Fairly large doses of alkalis (300 cc of 4 per cent sodium bicarbonate intravenously in one dose, and 1,600 cc of 5 per cent sodium bicarbonate per rectum over a period of three days—92 Gm in all) were employed to combat the extreme acidosis of the terminal stage, but this was only sufficient to raise the carbon dioxide capacity from 19 to 24 per cent by volume, still below her previous figures, so that one could not have expected to produce tetany from these therapeutic alkaline procedures.

The pathogenesis of the bone deformity is an even more interesting problem. Clinically the genu valgum, rachitic rosary and thickened epiphyses are difficult to differentiate from the similar deformities found in true rickets. Moreover, at the necropsy table microscopic examination of the costochondral junctions shows in some places an irregularity of the epiphyseal line with islands of osteoid tissue very similar to the picture seen in true rickets. However the roentgenogram shows nothing suggestive of rickets (fig 2). There is not the irregularity of the epiphyseal line that is seen in that disease, and there is none of the density of an old healing process such as would certainly be present with such a blood calcium and blood phosphorus as this case shows. The picture is merely that of delayed ossification. Moreover, the blood calcium and phosphorus are distinctly outside the rachitic zone, according to Howland and Kramer's figures¹¹. They have shown that in the vast majority of cases there is a calcification zone, when the product of the blood calcium and phosphorus is between 30 and 40, that with a product above 40 active rickets is excluded, and with a product below 30 rickets is almost invariably present. The products of 42, 43 and 54 in this case would seem to place these figures well above the rachitic level. The low calcium content of this patient's blood may possibly serve to explain the lack of calcium deposition in the bones, resulting in a softening of the long bones and in abnormalities of the epiphyseal growth. There is evidence to show that the late stages of renal insufficiency are often associated with an increase in the phosphorus content of the blood,¹² which is associated

10 Pincus, J. B. To be published.

11 Howland, J., and Kramer, B. *Proc. Am. Pediat. Soc.* **34**: 204, 1922.

12 Marriott, W. M., and Howland, J. *Phosphate Retention*, *Arch. Int. Med.* **18**: 708 (Nov.) 1916.

with a decrease in the calcium content. It may be that it is the extraordinary chronicity of the severe renal insufficiency with resulting low blood calcium in a growing person that permits the development of such abnormalities in the ossification of the bones.

In review, the sequence of events in a typical case of renal dwarfism may be pictured somewhat as follows. A severe renal insufficiency, usually a chronic interstitial nephritis, with no previous illness to excite suspicion, appears in a young child early in the second decade, at the onset of puberty before there is adult development of the osseous system. It seems that the renal lesions are of such a nature that they in some way influence mineral metabolism. That there is a disturbance in the normal relationship between the calcium and phosphorus content of the body fluids, which results in a profound alteration and delay in the normal bony development, we do know. Possibly this disturbance is primarily a phosphate retention, which appears to depress the calcium concentration of the blood. Aside from the defective osseous development and its consequences, the case runs the course of a severe chronic nephritis, with maximal nitrogen retention and, curiously, with little effect on the cardiovascular system. During the latter stages a rather severe acidosis appears, attributable in part to the phosphate retention. Death occurs in uremia before the end of the second decade.

SUMMARY

- 1 In the case of renal dwarfism reported here, the patient presented the picture of a severe renal insufficiency in association with a curious failure of the development of the bones.
- 2 Phosphate retention with resulting low blood calcium over a long period may be the cause of the delayed ossification of the bones.
- 3 The severe acidosis may have been the factor in causing the ionization of a sufficiently large proportion of the calcium to prevent the onset of tetany.

ARACHNIDISM

SPIDER POISONING

EMIL BOGEN, M D

LOS ANGELES

REPORT OF A TYPICAL CASE

One late summer evening, a young Mexican laborer, while sitting down in an infrequently used outdoor toilet in a suburb of Los Angeles, felt a sharp prick on the end of the glans penis. On looking down he saw a coarse web spun across the hole in the seat of the toilet, and a shiny black spider with a red spot on its belly scurrying to a corner of the web. After the first momentary stinging he felt no further pain in the penis, but about ten minutes later he began to feel a cramping, aching pain in the groins which rapidly spread over the abdomen, legs, back and chest, increasing in intensity for about an hour. He arrived at the Los Angeles General Hospital about six hours after the bite, writhing in agony, and complaining of nausea, vomiting, and of some difficulty in breathing.

The face was flushed, the pupils somewhat dilated, the respiration accelerated, and the knee jerks and other reflexes overactive. The abdominal wall was extremely rigid, suggesting the boardlike rigidity of a perforated gastric ulcer, although there was no marked local abdominal tenderness. A tiny red spot, barely discernible, marked the spot where he had been bitten. The temperature was normal on admission, but rose to 100.6 F by the next afternoon, while the pulse, which was 100 on admission, fell to 64. The blood pressure was 160 systolic and 90 diastolic, but fell to 130 systolic and 80 diastolic within twenty-four hours. A trace of albumin and a few hyaline casts were found in the urine. The patient had no bowel movements until after he had been given a cathartic on the second day, and he had some difficulty in voiding urine on the first day. The white blood count was 15,000 on admission, with 80 per cent of polymorphonuclear leukocytes, but this dropped to 9,000 by the third day, with 70 per cent of polymorphonuclears. The red blood count was normal, with a color index of 1.

Several hypodermic injections of morphine were given before the patient secured any relief from the pain, and an interrupted restless sleep followed the additional administration of 3 grains (0.1 Gm) of phenobarbital. The morning after admission he was bathed in a profuse cold sweat, and complained of more pains in the feet and legs, and a numbness that persisted for several days in the soles of the feet. By the second day he was able to sit up, and four days after the onset of symptoms he left the hospital, walking but still weak and afflicted by a little numbness and tingling of the feet.

THE LOS ANGELES GENERAL HOSPITAL SERIES

Fifteen patients have been treated for poisonous spider bites at the Los Angeles General Hospital in recent years. They were all males, ranging in age from 2 to 65 years, but more than half were young adults. Five were Mexican, one negro, two foreign born, and the other seven native whites. Six were common laborers, eight skilled workers, and one was an infant. Five of the bites occurred within the city of Los Angeles, the other ten in the suburbs. Most of them happened in the evening or early morning in the summer or early autumn. Thus, five occurred between 8 and 9, and four between 9 and 12 p m, and

one occurred at 3 and four between 8 and 11 a m There was only one instance each in April, May and October, but two patients were bitten in June, five in July, two in August and three in September The spider was located in a toilet in eleven instances, in a factory once, and in bed once Most of the patients had seen the actual spider, which they described as black and shiny, and several mentioned a red spot on its belly

The bite occurred on the penis in ten patients, the scrotum in two, the back in two, and the abdomen in one Local signs consisting of one or two tiny pink or red spots were found at the site in eight cases, and local symptoms in that region, after the first momentary prick, were complained of in five The chief symptom in every instance was pain This was described by seven patients as severe, by three patients each as continuous or aching, by two patients each as sharp, dull, stinging, cramping, or doubling up, and by others as considerable, great, burning, throbbing, cutting, tingling, shooting, rheumatic or generalized The pain was located in the legs in eleven cases and in the abdomen in nine, but was also in the chest, back, arms and penis in five cases each, and in the groin in three cases and all over in four

Perspiration, restlessness and vomiting were complained of by seven patients, constipation by six, nausea by four, difficulty in breathing by three, dizziness, chills, urinary retention, incoordination and edema of the face and of the legs by two, and hiccough, thirst and cough by one patient each Thirteen patients appeared to be in agony on admission, cyanosis was seen in five, the pupils were dilated in two, were small once and irregular once, and a heart murmur was heard in one The abdomen was rigid in twelve patients, but tender in only three The knee jerk and other reflexes were overactive in seven cases, tremors and twitching were found in four, and priapism was noted once

The pain appeared immediately in six cases and within a quarter of an hour in six others It reached the maximum severity within a quarter of an hour in three cases, in an hour in five cases, in two hours in three, and in four hours in two Three patients were seen at the hospital within two hours after the bite, four within six hours, five within twelve hours, and the others within forty-eight hours The diagnosis was not made definitely at the time of admission in the first five cases admitted, perhaps because we were not then familiar with the condition, for there has been no hesitancy in recognizing the last ten cases, eight of which occurred within the year 1925 The differential diagnosis included infection following insect bite, an acute surgical abdominal condition such as ruptured gastric ulcer or acute appendicitis with peritonitis, renal colic, food poisoning and lobar pneumonia

Eight patients had a subnormal temperature at the time of admission, but in nearly all a mild fever developed during their hospital stay, in

six instances reaching 100 F or more, but in no case going above 101.6 F. The pulse was generally retarded as compared with the temperature, being below 72 in half the patients on admission and falling below 66 in the majority during their first few days in the hospital. The respiratory rate was generally slightly accelerated on admission, but soon came down to 20, which was the average rate during the remainder of their stay in the hospital. Two patients had urinary retention requiring catheterization on the day of the bite, and almost all were constipated, going one, and in six cases two, days without a bowel movement.

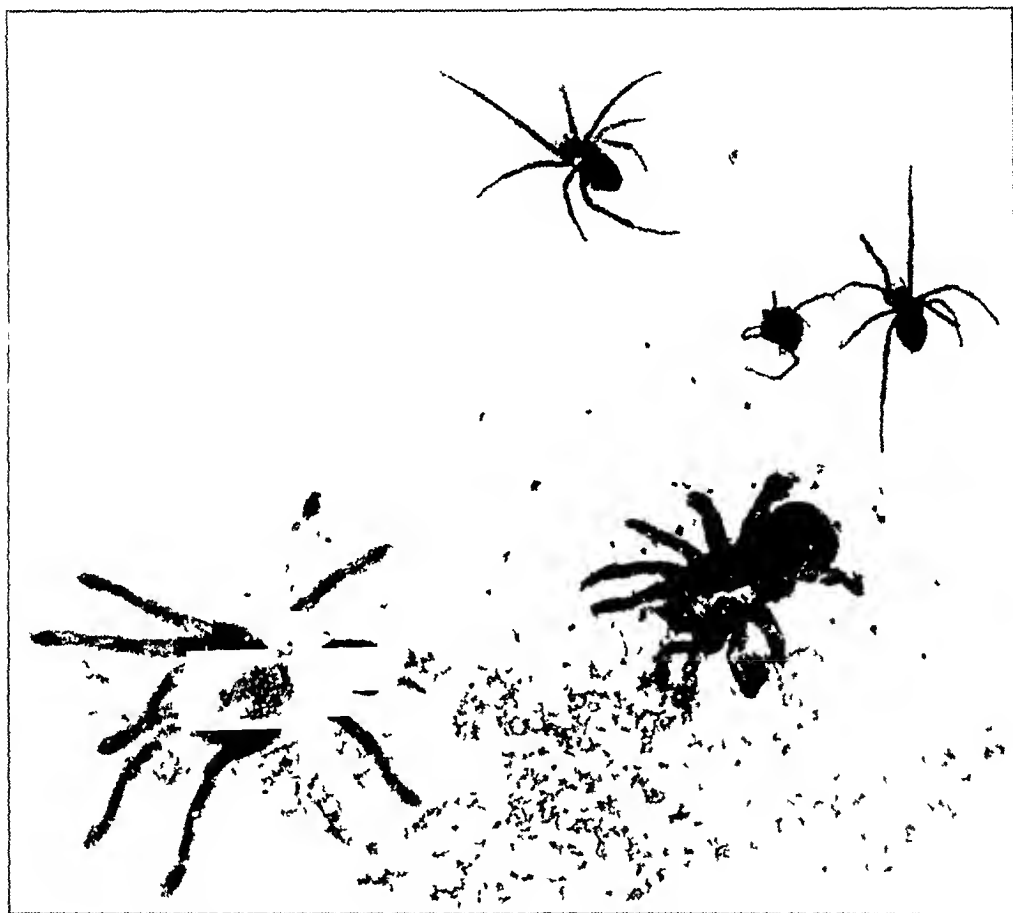


Fig. 1—A tarantula, a trap-door spider and three *Latrodectus mactans*

Hypertension was found in every patient examined, the blood pressure averaging 150 systolic and over 87 diastolic on admission. Repeated readings, however, showed a rapid drop, the systolic averaging only 136 on the day after admission. Urinalysis showed a trace of albumin in three cases, with hyaline or granular casts in four, pus cells in three and indican and blood in one case each. Stool examination revealed blood in one case. The Wassermann test was four plus in two cases, two plus in one, suspicious once and negative eight times. Leukocytosis was present in almost every case, averaging 14,761 in the nine cases examined on the day of admission, 11,600 in the five cases

examined on the second day, 10,720 in the four cases examined on the third day in the hospital, the highest count being 21,000 on admission, and the lowest 5,900 several days after the bite. There generally was a relative polymorphonuclear leukocytosis, averaging 80 per cent in the eight cases recorded. The red blood cell count was not constant, averaging 5,000,000 in the seven cases recorded, with an average hemoglobin estimation of about 85 per cent. Altogether more than sixty physicians saw these patients while they were in the hospital.

The treatment at the hospital consisted mainly of sedation, with morphine or codeine in ten cases, barbitol compounds in seven, hot applications in four, atropine and salicylates in two, and chloral and bromides in one case each, of stimulation, with aromatic spirits of ammonia in three cases, caffeine in two and strychnine once, and of elimination, with magnesium sulphate or citrate in seven cases, castor oil, sodium bicarbonate or enemas in three, and calomel or gastric lavage in one case each.

About six months ago it was felt that, even though we have not yet had a fatality at the Los Angeles General Hospital, it would be advisable to seek some more efficient mode of treatment, since these patients respond so poorly to opiates and require such large doses to give them relief. The use of convalescent serum was suggested, and accordingly 20 cc of blood, taken from a patient who had recovered from a severe poison spider bite inflicted ten days before, was given intramuscularly to a man who had just entered the hospital in the agony of pain from a spider bite. Since he seemed to be quite improved after the injection, a quantity of blood has been taken from all patients who recover from poisonous spider bites since then, and the serum separated and kept on ice for use in succeeding cases. Only four cases have been so treated up to the present time, but in each of these the relief was felt within a few hours after the injection, and comparative ease was afforded in a much shorter time than would have been expected.

REVIEW OF THE LITERATURE *

Despite the prevalent popular belief in the poisonous nature of spider bites, entomologists and arachnologists^{34, 89, 289, 434} have been almost unanimous in asserting that they are harmless, and medical men have been accused of unscientific readiness to accept popular reports of spider bite poisoning without establishing the truth of the facts stated^{105, 358}. A spider bite, as any other wound, may easily become infected, and so we find that undoubted cases of tetanus,²⁵¹ anthrax,¹⁵⁵ erysipelas,⁴⁴⁴ cellulitis³⁴⁸ and septicemia,¹²⁴ confirmed by necropsy and bacteriologic

* On account of lack of space, the bibliography to this article appears in the reprints only.

examinations, have arisen from spider bites. Moreover, the very measures adopted for the treatment of the spider bite may in themselves be the cause of some of the symptoms reported,⁵⁵ as the local sloughs following the injection of aqua ammonia,³⁸⁵ or the symptoms of intoxication following the free imbibition of "stimulants"^{11,2} and the possibility of coincidence must always be borne in mind.²¹⁴



Fig 2—*Latrodectus mactans*

Nevertheless, the positive evidence of hundreds of careful observers cannot be lightly disregarded. Dangerous illness and even death from the bite of *Latrodectus tenebrosus* have been repeatedly described in Spain,¹⁰⁷ France,^{93, 106, 177, 217} Italy⁷⁵ and Corsica^{76, 341}. Dozens of articles have recorded severe results from the bite of related species, *Katipo* in Australia^{140, 307, 331} and New Zealand,^{151, 360, 445, 458} *Karakant* in Southeastern Russia,^{241, 311, 336, 421} and *Mena vodi* in Mada-

gascar^{64, 146, 429} In South America the poisonous effects of the bite of spiders have been studied both in the clinic and in the laboratory by more than thirty writers. The South Americans describe necrotic, icterohemorrhagic and exanthematous forms of arachnidism caused by the bite of different varieties of spiders in the tropics but all agree that *Latrodectus mactans* causes only a neurotoxic form of the disease with little or no local phenomena^{2, 10, 131, 154, 155, 205, 255, 283, 395, 398}

THE LATRODECTUS MACTANS

Latrodectus mactans is the chief and perhaps the only really poisonous spider in the United States. Besides its many scientific synonyms,³³⁴ including the names *Latrodectus formidabilis*, *perfidus*, *dotatus*, *zonilla*, *intersector*, *apicalis*, *variegatus* and *thoracicus*, and *Theridium verecundum*, *lineatum* and *carolinum*, it has been given many popular nicknames, such as the "black widow,"²²⁸ the "hourglass" spider,²⁰⁴ the "shoe-button" spider, the "I bar" spider, the "po-ko-moo"²⁹⁵ and simply the "poison" spider. Although it is encountered mainly in the southern half of the United States, from the Atlantic to the Pacific coasts, specimens have been reported from such northern states as New Hampshire,⁸⁹ New York, Pennsylvania and Ohio.

Latrodectus mactans is a shiny, coal black spider, usually brilliantly marked with red or yellow or both. The female, which is always the one responsible for the bites reported, is often a half-inch in length when fully grown, and may stretch its slim glossy black legs over as much as 2 inches (5 cm). The markings vary greatly, the most constant being a bright red patch shaped somewhat like an hourglass, on the ventral surface of the abdomen. The globose abdomen, much larger than the cephalothorax, resembles a black shoebutton, although it may have one or more red spots along the middle of the back and over the spinnerets, in addition to the ventral patch. The male is much smaller than the female, and is even more conspicuously marked, having four stripes along each side of the abdomen, in addition to the marks of the female. The young spiders are much lighter in color, gradually donning the glossy black coat in a series of moults over about forty days.³⁰²

The black widow, as it is called from its custom of eating its mate, is usually found alone, as it will engage in mortal combat with any other spider placed near it. It builds a coarse and irregular dark web in dimly lighted places where it may be undisturbed. Occasionally it is found under stones or pieces of wood or in holes in the ground, in old stumps or bushes, more often in the rafters and corners of little used buildings, in the basements and attics of unfrequented houses, and in the dark corners of barns and other outbuildings, and it has been frequently seen in outdoor toilets, where it builds its web across the seat of the toilet.

AMERICAN CASES

More than 150 cases of poisonous spider bites have been reported by thirty-three physicians in the United States during the last century. Two thirds of these occurred in California, but the others were scattered over more than a dozen states, including Florida, Virginia, Georgia, North Carolina, Alabama, Texas, Oklahoma, Maryland, Pennsylvania, Tennessee, Ohio, West Virginia and Arkansas. More than 80 per cent of the victims were males, and the majority were bitten on the penis or adjacent parts while sitting in an outdoor toilet, others on the hands, feet or other exposed parts. All ages have been reported. A minister and a college professor have not been spared, but most of the victims were farmers or rural laborers, as might be expected from the habitat of the spider. Most of the bites occurred either in the early morning or in the evening in the summer or autumn, but this was not the invariable rule, as cases have been known in almost every month of the year. The spider actually causing the bite was captured and identified by arachnologists in about a dozen cases, but usually it was described as a shiny black spider, and the red spot on the abdomen was frequently mentioned.

A stinging or sticking sensation was noted at first, but this soon disappeared, and except for a tiny red spot sometimes seen, there was no mark or swelling to indicate the location of the bite. In less than half an hour, however, the characteristic pain appeared, increasing in severity for several hours. It has been vividly described as intense, violent, agonizing, exquisite, excruciating, griping, cramping, shooting, lancinating, aching and numbing, and was either continuous and incessant or paroxysmal and intermittent. It was felt in the abdomen and generally also in the legs, back, chest and "all over," less often in the head, shoulders and arms. The pain spreads from the site of the wound by continuity, thus, the patients bitten on the penis usually have pain in the groin and then in the abdomen, while those bitten on the wrist have pain in the arm and then the chest before it reaches the abdomen, suggesting that the venom spreads by the lymphatics and acts in the muscles rather than in the central nervous system. The final distribution of the pain, disregarding the order of development, however, appears to be fairly uniform, irrespective of the site of the initial lesion, and the pain in the abdomen and legs follows bites of the wrist or back just as regularly as it does those of the penis or ankle.

In addition to the acute pain, which was evidenced in most cases by writhing, rolling, doubling up, muscle spasms and paroxysmal contractions, many other symptoms were described. The most common, in the order of frequency, include profuse cold sweats, restlessness, anxiety, difficulty in breathing, anorexia, nausea and vomiting, constipation, cyanosis, delirium, prostration, shock, insomnia, speech dis-

turbances and acute urinary retention Tremors, twitching, paralyses, convulsions, localized swelling of the bitten part, or of other tissues, chills, dizziness, priapism, jaundice and a macular skin eruption were also encountered

An extreme boardlike rigidity of the abdomen was the most striking physical finding, but abdominal tenderness was rarely mentioned Circulatory disturbances, evidenced by cyanosis and an unduly slow or rapid pulse were often noted, but actual figures were lacking The patients were usually seen by the physician within a few hours after the bite, but the diagnosis was not always made at once, and in several instances the patient was operated on by mistake for an acute appendicitis⁴³⁸ or other acute surgical abdominal disease, while biliary or renal colic, acute pancreatitis, ruptured gastric ulcer and various forms of poisoning were suggested in others The most acute symptoms lasted a number of hours, no relief being felt for more than six hours in half the cases reported The pain then generally subsided in from twelve to forty-eight hours after the onset, but complete ease was often not secured for more than a week, and many complained of weakness and recurring pains for many weeks thereafter

Seldom in medicine will one find a greater diversity of therapy than in the recorded cases of spider bite More than seventy-five different remedies have been administered, each with the greatest apparent confidence that this was the best line of treatment Morphine, whisky or brandy, aqua ammonia or spirits of ammonia, atropine, magnesium sulphate, hot baths and fomentations, enemas, blood-letting, opium or tincture of opium, strychnine, camphor and potassium permanganate have been most commonly employed Among the other medications mentioned we find amber, arsenic, antimony, acetylsalicylic acid, aconitine, boneset, calomel, cantharides, cocaine, castor oil, Dover's powders, Darby's fluid, Echinacea, edgeweed, elaterium, glonoin, hyoscine, hoarhound, ipecac, lavender, mustard plasters, milk, magnesium phosphate, mercuric chloride, belladonna, nitroglycerin, olive oil, potassium acetate, iodide and carbonate, phenol, plantain, rue, quinine, sinapisms, spirits of turpentine, squirrel's ear, senna, sodium chloride, tansy, tartar emetic, tobacco poultice, valerian, volatile liniment, and Wizard oil

There is a widespread impression that *Latrodectus mactans* may cause death, and indeed this is not improbable The closely allied species, *Karakurt* in Russia, *Malmignatus* in Spain, and *Scelio* in New Zealand, have all been reported as causing considerable loss of life, and in South America many lethal cases have been reported About ten deaths have been definitely ascribed to the bite of *Latrodectus mactans* in the United States, but only a few of them, as the cases of Dick in North Carolina,¹¹² Reese in Oklahoma,³⁵⁴ and Clark in California,⁵⁶ have been described in detail Here the symptoms appear to have been

the usual ones, perhaps a little more severe, and death ensued in from fourteen to thirty-two hours. Heavy dosage with alcohol may have helped to bring on this fatal termination in certain cases, as has been stated, but this will hardly account for all. One victim had been bitten twice by the spider. However, no patient with spider bite has ever died at the Los Angeles General Hospital, nor can we find any record of a case coming to necropsy in the United States.

EXPERIMENTAL STUDIES

The literature of experimental studies of poisonous spider bites is highly conflicting and confusing. Walckenaer,⁴³⁴ Blackwall,³³ Duges,¹²¹ Doleschall,¹¹⁶ Bertkau,³¹ McCook²⁸⁹ and Simon³⁹² allowed themselves to be bitten by various spiders, and Lucas²⁶⁷ and Bordas³⁹ reported bites by *Latrodectus*, all stated that they were unable to detect any sign of systemic poisoning resulting from the bite. On the other hand, the



Fig. 3—Young male white rat bitten by female *Latrodectus mactans*. It developed a humped back, an almost paralytic gait and sluggish behavior, two days later it died.

careful experiments of Baerg,¹⁴ who received a spider bite on the finger under well controlled laboratory conditions, and reports most vividly on the severe symptoms that followed, which caused him to remain in the hospital for several days, are not lightly to be disregarded.

Injections of extracts, and transplants of the poison glands of *Latrodectus mactans* into rabbits and guinea-pigs without any effect²⁷¹ were reported by George Maix in 1889. A few years later, however, Frost reported causing death in one rat and severe symptoms in another with a bite from *Latrodectus scelia*, but that a dog was practically unaffected.¹⁵¹ Bieeger asserted that the poison of *Latrodectus karakurt* was sufficient to cause death in warm blooded animals in almost infinitesimal doses.⁵¹ In 1902 Rudolph Kobert reported that an extract of this spider was highly hemolytic and decidedly poisonous to dogs.²⁴⁰ About the same time Sachs,³⁶⁹ in Ehrlich's laboratory, reported an extensive series of experiments showing that the extract of the garden spider contains a powerful hemolysin. In 1914 Castelli⁷⁵ in Italy

stated that an extract of *Latrodectus tedeinguttatus* injected into rabbits and guinea-pigs produced death very quickly. The next year Coleman⁸⁷ of California stated that an extract of the poison gland of *Latrodectus mactans* caused convulsions and death in a cat, and that a suspension of the spider's eggs was lethal on injection into a cat and a rabbit. He also asserted that there were curious effects from the oral administration of a dry powder prepared from the gland, and attempted its use in therapy. In 1923 Baerg¹⁴ of Arkansas found that the bite of *Latrodectus mactans* produced a definite chain of symptoms in a young white rat, and that an immunity was developed after repeated bites.

In view of the contradictory results summarized above, it appeared desirable to repeat certain of the experiments and so obtain a first hand knowledge of the effects of spider poison on warm blooded animals. Repeated injections of macerated suspensions of *Latrodectus mactans*, as well as solutions of the expressed poison glands, were made in a number of animals, including rabbits, chickens, cats and white rats, without noticeable effect. There was no evidence of any hemolytic effect either in the tissue extract or the suspension of the poison gland as tested against the blood corpuscles of rabbit, sheep and man. The bite of the spider, however, produced the definite symptoms described by Baerg in a young rat, as may be illustrated by a report of a typical experiment.

Jan 8, 1926, a female *Latrodectus mactans* was applied to the penis of a young male white rat until it took a firm bite. The rat squealed at the bite, and a few minutes later it arched its back in a sort of a hump and appeared to be very dejected and depressed. The next day motion pictures were taken (fig 3), demonstrating the almost paralytic gait, humped back and sluggish behavior of the rat. Two days later it was found in the cage, dead and partially eaten by the other rats.

CONCLUSION

There is a peculiar, striking and characteristic chain of symptoms following the bite of *Latrodectus mactans*, a poisonous spider common in North America. An exhaustive examination of the available literature on poisonous spider bites in all corners of the earth and an analysis of 150 cases that have been reported in the United States have been attempted. The experimental studies previously made have been reviewed, and additional experiments performed to elucidate some of the moot points. Constant characteristic symptoms have been produced by the bite on a young white rat. It is concluded that the foregoing warrants the acceptance of arachnidism, or spider bite poisoning, as a true clinical entity in the field of general medicine.

NONTRAUMATIC LEFT DIAPHRAGMATIC HERNIA

CLINICAL AND ROENTGENOLOGIC STUDIES IN FIFTEEN CASES [†]

HENRY K PANCOAST, M D

AND

RUSSELL S BOLES, M D

PHILADELPHIA

In reviewing the literature on diaphragmatic hernia, it may be noted that the condition was discovered only seven times in 25,000 roentgenologic examinations, according to the separate reports of Beclere,¹ MacMillan,² and Rendich.³ The Mayo Clinic records finding twenty cases up to July, 1924, or one in about every 18,000 patients examined. According to Carman,⁴ fifteen of these were found in the years 1923 and 1924. Richards⁵ has tabulated 137 cases taken from the literature from 1900 to 1923. These were all nontraumatic and of the esophageal variety. It is worthy of note that up until 1923 only forty-seven cases had been diagnosed during life.

While these figures would create the impression that the condition is rare, this is not the case. The more general employment of the roentgen ray with its recent advances in diagnosis makes it apparent that diaphragmatic hernia has frequently been overlooked in the past. Morrison,⁶ for instance, detected forty-two diaphragmatic hernias in 3,500 roentgenologic examinations of the gastro-intestinal tract. It is proposed in this article to confine our remarks entirely to the question of nontraumatic hernia, fifteen cases of which, all on the left side, were observed and studied by us. In all, sixteen cases, which include one of traumatic origin, were discovered in approximately 9,000 gastric cases studied.

On the basis of an exhaustive embryologic study of the origin of these hernias, Richards⁵ has classified them as follows:

[†] From the University of Pennsylvania Hospital.

1 Beclere, quoted by Morrison, L. B. Diaphragmatic Hernia of Fundus of the Stomach Through Esophageal Hiatus, *J. A. M. A.* **84** 161 (Jan 17) 1925.

2 MacMillan, quoted by Morrison (footnote 1).

3 Rendich, quoted by Morrison (footnote 1).

4 Carman, R. D., and Fineman, Solomon. Roentgenologic Diagnosis of Diaphragmatic Hernia with a Report of Seventeen Cases, *Radiology* **3** 26 (July) 1924.

5 Richards, L. G. Nontraumatic Hernia of the Diaphragm. An Embryological Viewpoint, *Ann. Otol. Rhinol. & Laryngol.* **32** 1145 (Dec.) 1923.

6 Morrison, L. B. Diaphragmatic Hernia of Fundus of the Stomach Through the Esophageal Hiatus, *J. A. M. A.* **84** 161 (Jan 17) 1925.

- 1 True hernias (those with hernial sack)
 - (a) Congenital (present at birth)
 - (b) Acquired (through a natural opening, usually the esophagus)
 - (c) Elsewhere—traumatic or nontraumatic
- 2 False hernias (without sack)—90 per cent of cases
 - (a) Congenital
 - (b) Acquired (all traumatic)
- 3 Eventration of diaphragm (not true hernia)

Diaphragmatic hernia, as the name implies, is a protrusion of any of the abdominal viscera into the thoracic cavity through a congenital or an acquired opening in the diaphragm. The opening may be a normal one which has become enlarged, it may be an artificial one acquired by injury, or it may be present abnormally as a result of impaired development. Depending on whether the hernia has a sack or not, it is called true (with a sack) or false (without a sack). The sack when present consists of a layer of pleura or peritoneum or both. The true and the false type of hernia may be congenital or acquired. By far the commonest type is the congenital false variety, which comprises 90 per cent of the congenital type of diaphragmatic hernias. The acquired false hernias are all traumatic, and are ordinarily thought to be the most common type, although in the present series of cases in only one could a history of trauma be elicited. They therefore are considered congenital. LeWald believes that all cases in which an abdominal viscus is found in the thoracic cavity should be regarded as congenital unless there is overwhelming evidence that the condition has been acquired. It is generally accepted that false hernias develop as the result of a defect in the diaphragm, which is thought to be due to imperfect closure during fetal life of the pleuroperitoneal membrane. In the cases of the true hernia, the arrest in the development of the diaphragm occurs at a later period when the muscle is still too weak to offer any resistance, but after the pleura and peritoneum have formed. These structures consequently are involved in the resulting protrusion into the thorax, and make up the sack which establishes the true type.

The abnormal development of the diaphragm in the true type of hernia is thought to be due to a pathologic rather than to a purely embryologic disturbance such as occurs in the false hernias. Nontraumatic hernia, particularly of the congenital type, has been thought to occur less frequently than traumatic. In this series of cases, however, all were nontraumatic but one. Partially because of the absence of trauma this type is invariably unsuspected and rarely discovered except accidentally. True hernias of the esophageal variety, according to Tonndorf,⁷ are due to a malformation developing at a very early embry-

⁷ Tonndorf, F. Hernia of the Diaphragm as a Result of Inhibition of Growth of the Esophagus, *Deutsche Ztschr f Chir* **179** 259 (May) 1923

omic period from an inhibition of the growth of the esophagus. He bases this deduction on the anatomic observations in four cases in which dissection was performed. In all four, the esophageal opening formed the hernial ring, and in all the shortened esophagus emptied into the hernia sack. This author suggests that all false hernias, because of the absence of the sack, might more correctly be termed prolapses, or ectopias. Le Wald⁸ calls attention to a condition that he terms thoracic stomach. This is a congenital anomaly, and refers to a stomach that develops above the diaphragm and is never found below it. In such cases, it may be shown roentgenologically that the esophagus does not pass through the diaphragm, and no other organs of the abdomen are ever found in the thorax. He emphasizes the importance of differentiating thoracic stomach from eventration. In the latter condition, the stomach is always below the diaphragm, which is considerably elevated.

One might justly get the impression from a review of the literature that any part of the diaphragm is susceptible to herniation, especially any of the natural openings. As a matter of fact, a true hernia through the aortic opening or through the quadrilateral foramen which serves as the opening for the inferior vena cava has never been seen. The great majority of hernias are through openings on the left side of the diaphragm (the ratio to the right side being as 12:1) and they may be either anterior, central, or posterior. According to the report of cases diagnosed, and especially those that come to operation, the esophageal variety is the most common. In this series, twelve of the cases were of the esophageal type, three were central, and one was probably central. Richards believes, however, that the esophageal type is uncommon.

Why the left side of the diaphragm is the usual site for a hernia is not definitely understood. It may be partially explained by the fact that protection is afforded the right side of the diaphragm by the liver below and the right lung above. The free motility of the stomach tends to expose the left side, which is already weakened because it contains the natural openings and because it is formed to accommodate the spleen and the stomach. Furthermore, there are two fibrous bands present on the right side of the diaphragm which reinforce it. In addition to these conditions there are probably embryologic abnormalities present, the nature of which is undetermined. This is especially to be considered in the more frequent left sided hernias, as the formation of this side of the diaphragm is considerably more complicated in the embryo than that of the right side. The theory has been advanced, for instance, that as the left side closes after the right and is consequently more poorly vascularized, but little pressure from the abdominal viscera would be required to interfere with its nourishment and thereby arrest its development.

⁸ LeWald, L. T. Thoracic Stomach. Differentiation from Eventration and Hernia of the Diaphragm, *Radiology* 3:91 (Aug.) 1924.

Practically every organ in the abdomen, with the exception of the rectum and urogenital organs, has been known to herniate through the diaphragm. More commonly the stomach, colon or both are found to migrate to the thoracic cavity. In this series of fifteen cases, thirteen involved the stomach alone, one, all of the colon except the descending portion and sigmoid, and one, the stomach and colon.

Displacement of organs normally situated in the thoracic cavity usually occurs as a result of the pressure exerted by the herniated organs. The detection of such displacements should lead one to suspect the presence of diaphragmatic hernia. Because of the frequency of left sided hernias, displacement of the heart toward the right and collapse of the left side of the left lung are the most commonly observed changes in the visceral relations. Secondary herniation through the posterior or anterior mediastinal tissues may ensue, in which case an abdominal viscus herniating through the left side of the diaphragm may be found in the right side of the thoracic cavity.

SYMPTOMS

Symptoms may be entirely absent. If present, as is usually the case, they may be respiratory or gastric in nature. More often they are gastric and suggest disease of the gastro-intestinal tract. As a rule these patients are thought to have peptic ulcer, cholecystitis or carcinoma. If the symptoms are mainly respiratory, cardiovascular disease is usually suspected. Probably the most constant, certainly the most suggestive, symptom present is pain, often of a colicky nature, localized just above the ensiform or in the epigastrium, which comes on gradually and more often when the patient is lying down, especially at night. This point emphasizes a none too well recognized fact, i. e., the importance of eliciting an exhaustive history. The pain may be so severe as to suggest biliary colic, and is apt to radiate through to the back and around to the shoulders. Tenderness is noted in the right upper quadrant, or less frequently in the epigastrium. Regurgitation, especially when in the supine position, frequently occurs, probably as a result of the patent cardio-esophageal opening that is usually found in the esophageal hernias. Morrison⁶ found such a patency in all of the series of forty-two cases he reported. It furthermore explains, as he points out, why some patients with these hernias cannot sleep on the back or on the left side without acid regurgitation. At times vomiting, especially in the early morning is complained of and may give temporary relief. The appetite may be unimpaired and dysphagia is relatively infrequent. Excessive flatulence and belching are commonly present two or three hours after meals. Hematemesis, which further encouraged the diagnosis of ulcer, may occur and may be due to inflammation of that part of the stomach wall.

that is involved in the opening. Such cardiorespiratory symptoms as dyspnea and palpitation, which at times may occasion no little anxiety, are less frequently present. They are more apt to be noted in elderly people and especially those with myocardial disease, cardiac hypertrophy and aortitis.

PHYSICAL SIGNS

Physical signs may be absent, particularly in the esophageal opening hernias. Frequently asymmetry of the chest with protrusion of the affected side and displacement of the heart or lungs may be observed. A horizontal area of dulness, which is not absolute, or tympany at the lower boundary of the lung may be found on percussing the patient in the erect position. The area of dulness may move downward with inspiration. The respiratory sounds may be preserved over a hernia, and metallic phenomena as described by Elias and Hitzengerber⁹ are to be found in certain cases. Vocal fremitus is usually diminished over the affected area.

DIAGNOSIS

The diagnosis has seldom been made clinically. It can readily be made by the roentgenologist, however, and if made early the patient will often be spared an unnecessary operation for some other suspected cause of his illness. Misleading symptoms which direct suspicion and treatment toward innocent organs invite delay, and the danger of strangulation, even if not great, is always present and greatly adds to the mortality of operation. In making a roentgen-ray diagnosis, the examination should be made after a barium meal, first with the patient in the erect position, thus obtaining anteroposterior and oblique views, and then observations should always be made in the horizontal position. It appears that these hernias are frequently overlooked because the fundus is not filled and the patient's position changed. Repeated attempts to fill the herniated portion of the stomach may be necessary, and more than one examination required. Subsequent examinations of the colon should be made to determine whether or not it is included in the hernia. The roentgenologist can help determine the type of treatment by observing the size and location of the hernia and by noting the symptoms when the hernial sack is filled, and the amount of dilatation of the esophagus. The examination should suggest the site for operation, whether above or below the diaphragm, by determining the position of the diaphragm, the width of the angle at the ensiform, and the extent of ossification seen in the costochondral cartilage. In making roentgen-ray examinations the length of the esophagus may sometimes be determined, but esophagoscopy

⁹ Elias, H., and Hitzengerber, K. Comparative Examinations of Patients by Clinical and Roentgenologic Methods. Diagnosis of Hernia and Relaxation of the Diaphragm, *Wien Arch f inn Med* 6:437 (July 1) 1923.

is the only exact way of determining this in many cases. Patients with a congenitally short esophagus of course are not amenable to surgery. Much of interest from a roentgenologic standpoint, particularly the diagnosis, has been contributed by Carman and Fineman,⁴ Reich,¹⁰ LeWald,⁸ Ford¹¹ and Healy¹²

ROENTGENOLOGIC REPORT OF CASES

In reporting the roentgen-ray findings in the case of esophageal opening hernia of the stomach under discussion, it has seemed worth while to include with this report a record of all the cases of diaphragmatic hernia which have been diagnosed by one of us, and which, so far as we have been able to learn, have never been formally reported. The records of the Department of Roentgenology of the University Hospital show that sixteen cases of left sided diaphragmatic hernia were observed during the last thirteen years, since comprehensive routine fluoroscopic studies have been carried out on gastro-intestinal patients in all necessary postures. This does not include any cases of right sided diaphragmatic hernia. Nearly all the hernias, as is usually the case, were discovered accidentally during routine gastro-intestinal studies. Three hernias through the central portion of the diaphragm were suspected because of findings in chest examinations, and were subsequently studied by opaque meals. One other patient was known to have a hernia and consented to a gastro-intestinal observation to satisfy our curiosity. One central case was traumatic and the other fifteen were congenital. Of all the cases, five were hernias through the central portion and eleven were through the esophageal opening. The latter groups can apparently be divided into two varieties, those in which the esophagus opens below the herniated portion and those in which it opens into the herniated portion of the stomach, the latter seeming to favor larger hernias.

In all the older cases, our roentgenographic records were glass plates which have been broken or have since disappeared. Fortunately lantern slides were made in most instances, and serve to show the condition.

CASE 1—Mrs W A B, aged 61, was examined Dec 21, 1925. This case is mentioned first for the reason that it was the one that suggested this presentation of the subject. The roentgen-ray examination was made by the double meal method. There was no six hour residue. In the erect posture the stomach was normal in position, size and shape, with the greater curvature at the umbilical level. No peristalsis or motility was observed until the stomach was palpated vigorously, and both then started at a normal intensity and rate. No defects in outline were noted except that in the prone, recumbent and right lateral recumbent postures there was observed an esophageal opening hernia of the stomach.

10 Reich, Leo. Roentgen Diagnosis of Diaphragmatic Hernia and Related Clinical Pictures of the Diaphragm, *Wien Arch f inn Med* **6** 445 (July 1) 1923

11 Ford, Charles. Diaphragmatic Hernia, *Radiology* **5** 158 (Aug) 1925

12 Healy, T R. Symptoms Observed in Fifty-Three Cases of Nontraumatic Diaphragmatic Hernia, *Am J Roentgenol* **13** 266 (March) 1925

about the size of an egg, above the left diaphragm (figs 1 and 2) The location of the esophageal entrance into the stomach could not be determined in relation to the herniated portion as there was no regurgitation of food into the esophagus and the hernia could not be seen in the erect posture There was no esophageal obstruction to either liquids or capsule The colon in this case was not included in the hernia

CASE 2—J B, aged 28, was examined Jan 13, 1915 This was a traumatic case through the more central portion of the left diaphragm In the recumbent posture about half the stomach was above the left diaphragm level Details are omitted as our report was not intended to include traumatic cases

CASE 3—Mrs W S H, aged 44, was examined March 13, 1915 This patient was referred for a chest examination She knew she had a left diaphragmatic hernia from previous examinations, and permitted us to examine her stomach as

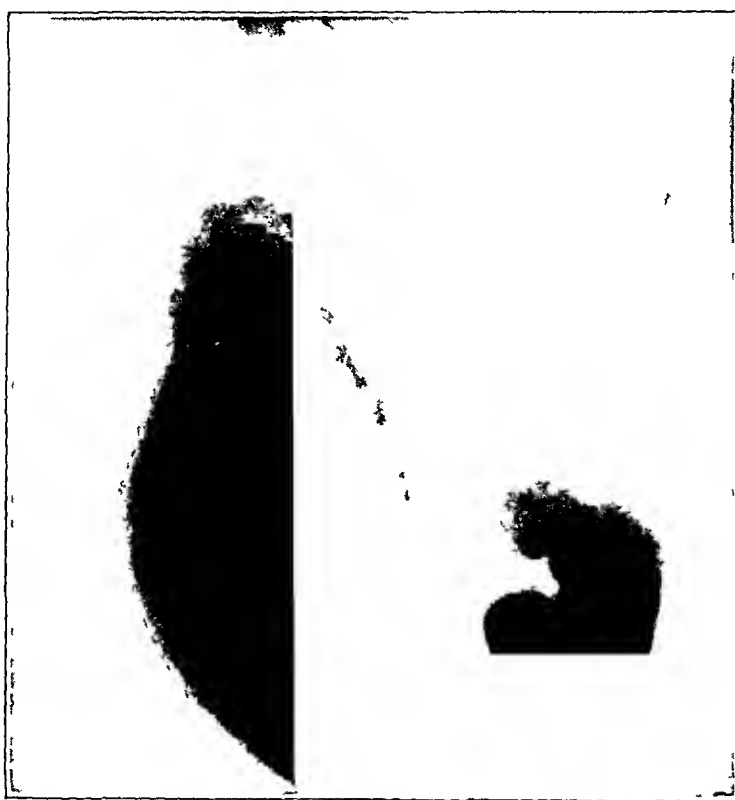


Fig 1 (case 1) —Appearance in erect posture, directly after opaque meal

a matter of interest By fluoroscope there was revealed in the erect posture a hernia of the upper portion of the stomach through the left diaphragm The herniated portion seemed to fill directly from the esophagus After the swallowing of the meal was completed, the pouch above the diaphragm emptied rather rapidly but filled again in the recumbent and prone postures, only to empty again on the patient's resuming the erect posture We were never able to satisfy ourselves entirely as to whether this was a small central or a large esophageal opening hernia, although appearances favored the former

CASE 4—Mrs H C I, aged 66, was examined April 14, 1915 She had had indefinite gastric symptoms for several years and ulcer or carcinoma had been suspected The opaque meal seemed at first to enter the stomach a considerable distance below the fundus, but a little later, there was observed a left diaphragmatic hernia of the stomach The herniated portion in the erect posture contained

only gas, but quickly filled with the opaque meal when the patient lay on her back or right side and emptied when she lay prone. No other abnormality was found. The colon was not included in this central hernia.

CASE 5—J. M., aged 13, was examined July 19, 1917. This patient was referred for a chest examination because of chest symptoms and signs. Further than this we are not able to obtain any clinical data. The fluoroscopic record reveals that gas was detected above the left diaphragm, and the patient was then given an opaque meal in the erect posture. It entered the stomach below the diaphragm. A lantern slide shows a small part of the meal and a large collection of gas above the diaphragm in the erect posture. When the patient was placed prone, apparently all the opaque meal was above the diaphragm, and the herniated stomach occupied the lower half of the left chest. Part of the colon was also found above the diaphragm. This was a central hernia.



Fig. 2 (case 1)—Appearance in recumbent posture, showing esophageal opening hernia.

CASE 6—Mrs. A. A. M., aged 65, was examined Sept. 19, 1918. The stomach was normal in position, size and shape, except that in the prone posture there was noted a small esophageal opening hernia, not evident in the erect posture. The stomach was otherwise negative and there was no esophageal obstruction. The location of the esophageal entrance into the stomach was not recorded.

CASE 7—C. O. B., a man, aged 55, was examined Dec. 11, 1919. He had a history of indefinite gastric symptoms. The stomach was normal in position, size and shape, and otherwise negative except that in the prone posture an esophageal opening hernia about the size of an egg was noted above the left diaphragm. From this, contents seemed to regurgitate directly into the esophagus quite frequently. There was no esophageal obstruction.

CASE 8—Mrs R E R, aged 68, was examined April 2, 1923 She had indefinite gastric symptoms The stomach was normal in position, size and shape and otherwise negative except that in the prone posture there was noted a moderate sized esophageal opening hernia above the left diaphragm level There was no esophageal obstruction

CASE 9—Mrs F W F, aged 60, was examined Feb 6, 1924 Vague gastric symptoms were complained of The stomach was normal in position, size and shape in the erect posture In the prone and recumbent postures, the fluoroscopic appearance suggested an hour glass constriction just below the fundus, and opposite to it, on the lesser curvature, a Haudek niche The stomach was otherwise negative and there was nothing abnormal in connection with the swallowing



Fig 3 (case 12) —Chest that presented an appearance suggesting a possible left sided diaphragmatic hernia

function The films showed that what was taken for an hour glass constriction was the narrowing at the neck of a rather large esophageal opening hernia above the left diaphragm The supposed Haudek niche was the entrance of the esophagus just below the constriction

CASE 10—J E, a man, aged 54, was examined Nov 27, 1924 His symptoms were mostly intestinal With the swallowing of the opaque meal, there was apparently an obstruction of a spasmodic nature in the lower end of the esophagus This was explained later, however, by the ease of regurgitation of food into the esophagus The stomach was normal in position, size and shape and otherwise negative except that in the lying positions there appeared an esophageal opening

hernia through a rather large opening, as the gastric constriction was slight. Our interpretation was a comparatively small hernia of the stomach into which a dilated esophagus entered, and in the absence of any diaphragmatic pinch cock, regurgitation occurred very readily on lying down. An esophagoscopy examination by Dr. Chevalier Jackson showed that gastric mucosa began about 6 inches (152 cm) below the left bronchus crossing. The herniated portion of the stomach was more extensive, therefore, than we thought. We could not tell where the esophagus stopped and the stomach began, or how much we interpreted as dilated esophagus was really stomach.

CASE 11—C. R. S., a woman, aged 50, was examined Jan. 8, 1925. She was suffering from indefinite gastric symptoms. The stomach was normal in position,



Fig. 4 (case 12)—Extreme ptosis of the stomach

size and shape, with the greater curvature slightly above the umbilicus. No defects were seen in the stomach or duodenal cap, except that in the recumbent posture a small esophageal opening hernia was observed. The esophagus opened into this portion.

CASE 12—R. C., a man, aged 27, was examined Jan. 8, 1925. His chief complaint was epigastric pain of several years' duration and recent pain in the right lower chest. An examination of the chest showed at the left base an appearance that suggested a possible diaphragmatic hernia (fig. 3). A gastrointestinal examination was then carried out. The examination of the stomach

showed practically a complete six hour residue and we were surprised to find no hernia of this structure in any posture but, instead, a long, low, vertical stomach with the greater curvature on a level with the symphysis pubes. There was a marked intermittent hyperperistalsis with antiperistalsis and no motility, except that in the right lateral recumbent posture it was fairly free. This indicated no pyloric stenosis but suggested that the obstruction was probably mechanical, due to kinking (fig 4). On the following day, most of the opaque contents in the colon were found in the thoracic cavity. A subsequent barium enema showed all the colon except the descending portion and sigmoid to be herniated through the left diaphragm (fig 5). After evacuation, the entire large bowel was empty of opaque contents. This case is unusual in the fact that the colon was herniated and the stomach was extremely ptosed. The ileum was never located.

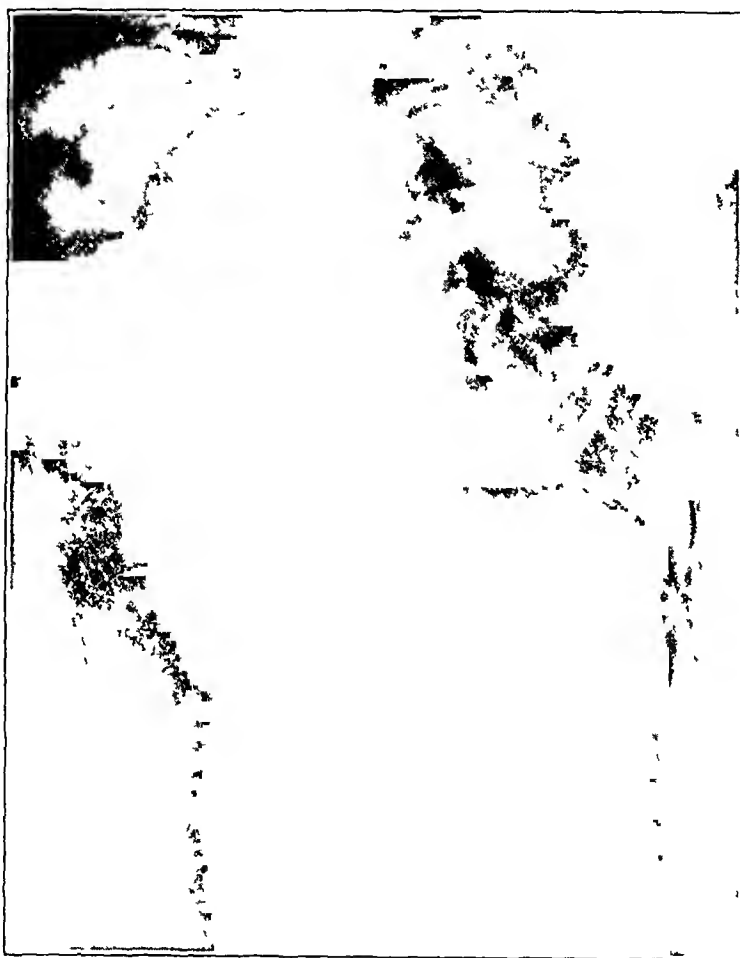


Fig 5 (case 12) —Appearance after barium enema, showing most of the colon herniated into the thoracic cavity through the left side of the diaphragm

CASE 13—Mrs L. C., aged 49, was examined March 24, 1925. This was a case of carcinomaphobia. The stomach examination was negative except for a small esophageal opening hernia, observed in only the prone and recumbent postures. The point of entrance of the esophagus in relation to the herniated portion of the stomach was not established.

CASE 14—I. M., a woman, aged 42, was examined Feb 15, 1926. This was at first regarded as a case of esophageal opening hernia, but a careful examination showed that what was taken for a herniated portion of the stomach was a large diverticulum coming off from the anterior and right aspect of the esophagus just above the left diaphragm. The diaphragmatic opening was large, without pinch-

cock effect, and it was impossible to tell just where the esophagus ended and the stomach began

CASE 15—Mrs B, aged 51, was examined April 7, 1926 The patient had been complaining of gastric distress and gaseous distention with eructations The examination of the stomach showed slight ptosis, but was otherwise negative, except that in the prone and recumbent postures, there was a small esophageal opening hernia The swallowing function was normal

CASE 16—Mrs C F H, aged 29, was examined March 18, 1926 She had complained for several years of epigastric distention after eating Epigastric pain appeared for three or four weeks at a time The pain was irregular in relation to meals There was considerable belching but no nausea or vomiting She felt more comfortable when lying down The pain frequently came on while the patient was eating, and was accompanied with vertigo The physical examination revealed nothing of significance Roentgenologic examination showed a cascade stomach causing almost an hour glass constriction There was a tendency for gas to collect in the fundus because of the high left diaphragm When the patient lay in the recumbent postures, the contents seemed to regurgitate into the esophagus The film indicated a moderate sized esophageal opening hernia There were multiple points of stasis in the small intestine suggesting slight obstruction Examination of the colon by barium enema revealed a redundant sigmoid loop, and a very high splenic flexure and transverse colon, which was probably responsible for the cascade stomach There was a spastic descending colon and upper sigmoid and a large capacious lower sigmoid and rectum

TREATMENT

There is only one line of treatment for diaphragmatic hernia and that is surgical Contrary to a widely prevalent belief, operation for this condition is not fraught with the risks commonly attributed to it The contraindications to operation are greatly overrated, according to Hedblom¹³ This author made a study of 378 patients that came to operation, and believes that while contraindications to surgery do exist, they are not great in comparison with the incapacitation the hernia produces or with the menace to life which its presence involves It has been estimated that in 15 per cent of cases strangulation occurs and as a result the operative mortality is doubled In a review of 126 cases in which obstruction ensued, the operative mortality was estimated at 53.1 per cent, in 252 cases without obstruction, it was 23.8 per cent The mortality in most instances was due to delayed operation in the presence of obstruction, to shock, and to respiratory failure In considering the approach for operation, it appears, if obstruction is excluded, that the mortality is greater following laparotomy than thoracotomy It seems, however, that most surgeons prefer laparotomy despite the fact that the dangers from thoracotomy have been reduced to a minimum Deaver and Ashhurst¹⁴ strongly urge thoracotomy They believe the prospects of recovery are better as the result of thoracic approach, as the lung is

13 Hedblom, C A Diaphragmatic Hernia A Study of 378 Cases in Which Operation Was Performed, *J A M A* 86 947 (Sept 26) 1925

14 Deaver, J B, and Ashhurst, A P C Surgery of the Upper Abdomen, Ed 2, Philadelphia, P Blakiston's Son & Co, p 242

already collapsed and the heart displaced. Of still more importance, however, is the fact that the existence of negative pressure in the unopened pleural cavity produces suction on the herniated organs, which makes reduction by traction below difficult and dangerous. They believe that laparotomy should be performed only when injury to some abdominal organs may have occurred, in which case an abdominal approach is required to effect their repair. Weichert¹⁵ and others prefer a combined thoracic and abdominal approach. The choice of operation must depend, however, on the nature of the case.

Disregarding the indications that compel operative intervention, such as strangulation and obstruction, it would seem reasonable *not* to operate in cases that are of congenital origin or in those of presumably long standing, especially if they are nontraumatic. In known traumatic cases, early reduction unquestionably is to be advised. In estimating the prognosis in cases in which no operation is done, it is interesting to note that ulceration of a herniated stomach may occur. Kienbock¹⁶ reported thirty-two such cases. In a few instances the ulcer has been known to perforate, thereby causing pyothorax. Peritonitis does not develop under these circumstances, since the abdominal cavity is protected by the muscular lining about the diaphragmatic opening.

In the final analysis, one must appreciate that the presence of abdominal viscera in the thoracic cavity not only is compatible with life, but, what is more amazing, may occasion none or but passing symptoms, and usually is discovered only accidentally at operation for some other condition or at necropsy.

SUMMARY

Diaphragmatic hernia is not as rare as is commonly thought. The more general employment of the roentgen ray with its recent advances in diagnosis make it apparent that the condition has been frequently overlooked.

Sixteen cases were discovered by one of us in approximately 9,000 gastric cases studied. Fifteen were nontraumatic and on the left side. Twelve were through the esophageal opening. Three were central, and one was probably central.

The diagnosis can be made with certainty only by means of the roentgen-ray studies. In the roentgenographic examination of gastrointestinal cases the studies should be made after a barium meal, first with the patient in the erect position, thus obtaining anteroposterior and oblique views, and then observations should always be made in the horizontal position. More than one examination may be required. Sub-

15 Weichert, Max. Operation for Diaphragmatic Hernia, *Beitr z klin Chir* **131** 180, 1924.

16 Kienbock. *Fortschr a d Geb d Rontgenstrahlen*, 1914, p 322.

sequent studies of the colon should be made in order to determine whether or not it is included in the hernia

The symptoms may be respiratory but are usually gastro-intestinal. The most common and suggestive symptom is pain above the ensiform or in the epigastrium, which comes on particularly in the recumbent position and at night time. Regurgitation when in the supine position usually accompanies the pain.

The recognition of the presence of diaphragmatic hernia is of great value in saving many patients an unnecessary operation for cholecystitis, peptic ulcer, and other common lesions which are often thought to be the cause of their symptoms.

Surgery offers the only line of treatment.

THE REGULATION OF THE FLOW OF BILE AND PANCREATIC JUICE INTO THE DUODENUM^{*}

GLOVER H COPHER, M D

AND

SHUICHI KODAMA, M D

ST LOUIS

Early in our study of the physiology of the biliary tract we were impressed with the considerable influence that the mechanism at the distal end of the common bile duct exerts, not only over the discharge of bile from the common duct into the duodenum but also over the gallbladder. In a previous article it was shown by one of us¹ that the control over the distal end of the common duct is one of the necessary factors for the collection of bile by the gallbladder. This article, one of a series of papers on the liver and biliary tract which have appeared from this department of surgery during the last five years, will report observations concerning some factors involved in the regulation of the flow of bile into the duodenum. A method of the regulation of the flow of pancreatic juice into the duodenum will also be described.

The presence of a control over the flow of bile is evident from the fact that bile may pass intermittently from the common duct into the intestine. This control has been considered by most investigators to be exerted almost wholly by the so-called sphincter of Oddi. A distinct sphincter cannot always be found apart from the fibers of the muscle coat of the intestine. However, it is the opinion of most investigators that such a distinct group of muscle fibers, which could act as a sphincter, is present in most animals and in man. A great many determinations have been made of the pressure in the common duct that the sphincter will withstand. Accurate determination of the pressure, which may be attributed to a common duct sphincter alone, is difficult to obtain because of a considerable number of sources of error.

Our attention was called to the fact that normal tonus of the duodenal wall might be an important factor in the resistance to the flow of bile into the duodenum by observing discharges of bile from the duodenal papilla coincidentally with the passage of peristaltic movements along the duodenum of a dog dying of anoxemia. Irritation of the cyanotic intestine caused vigorous peristaltic movements to form in the duodenum which were accompanied by an ejection of bile. Subsequent

^{*} From the Department of Surgery, Washington University School of Medicine and Barnes Hospital.

¹ Copher, G H. Cholecystography. Appearance and Disappearance of the Shadow, J A M A **84** 1563 (May 23) 1925.

confirmatory experiments were made by opening the duodenum of anesthetized dogs and visualizing the discharge of bile from the papilla with the passage of peristaltic movements initiated by various stimuli. The animal should be fasting previous to this experiment.

During the period of further investigation of this phenomenon, Burget² reported his experiments in which he measured the pressure in the common bile duct and observed the tonicity of the intestines. He is of the opinion that undue significance is attributed to the sphincter of the common bile duct. He concludes also that resistance to pressure in the common duct is offered by the normal tonus of the duodenum and that peristalsis of the duodenum is an important factor in emptying the duct by a milking action and by aspiration due to reduced pressure following a peristaltic wave. Pilocarpine and physostigmine were found through their effect on the tonus of the intestine, to increase greatly the amount of pressure withstood in the duct, while epinephrine and atropine reduced it to a minimum. Burget recognized the significance of the fact that the duct passes obliquely through the intestinal wall.

The common bile duct of the dog runs for a distance of from 2 to 4 cm obliquely through the wall of the intestine before it enters the lumen. The common bile duct in the human being together with the pancreatic duct perforates the muscular wall of the duodenum and runs obliquely for 1 or 2 cm between the coats to form an elevation beneath the mucous membrane. In most instances it opens by a common orifice with the pancreatic duct near the junction of the second and third portion of the duodenum.³ This anatomic arrangement will be shown to constitute a sphincter-like mechanism which is dependent on the tonicity of the intestine and makes it possible for peristalsis to be a factor in emptying the duct.

Carlson⁴ is also of the opinion that "the resistance to the flow of bile into the duodenum is probably determined more by the tonus of the muscle wall of the duodenum than by the tonus of the so-called sphincter of Oddi." He does not give experimental data but describes the anatomic relationship of the duct and intestine.

We have performed experiments in which a cannula was placed in the common bile duct of dogs at a considerable distance proximal to the point where the duct entered the intestine. Lateral hepatic ducts, which in the dog join the common duct below the cystic duct, were ligated. Pressure was maintained in the common bile duct by a column of

² Burget, G. E. The Regulation of the Flow of Bile, *Am J Physiol* **74** 585 (Nov) 1925.

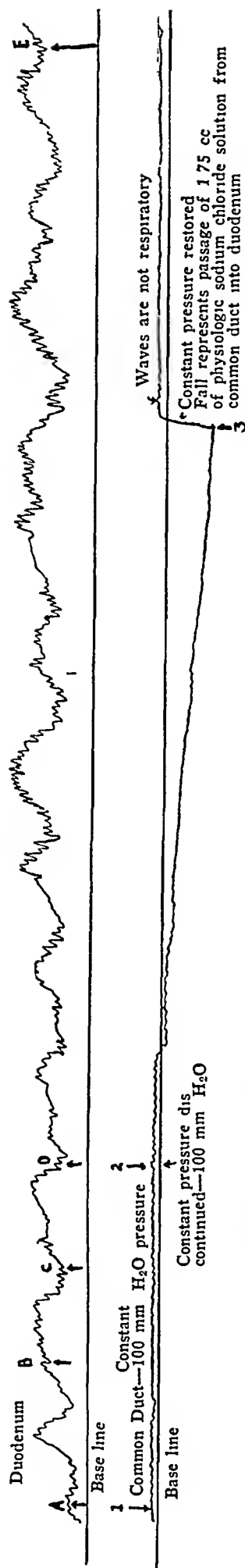
³ Quain's *Anatomy*, ed 10, New York, Longmans, Green & Co., part IV, **3** 128, 141.

⁴ Carlson, A. J. *Physiology of the Liver*. Present Status of Our Knowledge, *J A M A* **85** 1468 (Nov 7) 1925.

fluid in a buret which was connected to the cannula in the duct. A pressure of from 50 to 250 mm of a physiologic sodium chloride solution which varied with each dog was maintained. Variations of pressure and volume in the duct were observed in the buret. They were also recorded by a tambour on a smoked drum. The duodenum was ligated both near the pylorus and approximately 6 cm below the duodenal papilla. The pancreatic ducts were ligated. Tonus, movements and changes of volume in the portion of duodenum between ligatures were recorded on the drum by means of a glass tube containing physiologic sodium chloride solution, which was held in the intestine by a purse string suture. The results were the same whether we used physiologic sodium chloride solution, bile or a gum arabic solution of approximately the same viscosity as bile. These experiments differ from those of Buiget in that not only the pressure in the common duct is measured but also the amount of discharge from the duct. Likewise, changes of tonus and volume in the duodenum were recorded simultaneously with those of the common duct.

A fall of the pressure in the common duct was found to accompany relaxation of tonus of that portion of the duodenum containing intramural duct. Relaxation of the tonus may occur independently of peristalsis. The discharge of the content of the common bile duct into the duodenum may take place during the relaxation phase of a peristaltic movement. This relaxation occurs either with spontaneous peristalsis or induced peristalsis originating from chemical, thermal, mechanical or electrical stimuli. Coincidentally, with the fall of pressure in the common duct and the passage into the duodenum of physiologic sodium chloride solution there was usually recorded an increase in volume of the duodenal content (accompanying figure). This increase in volume would not be recorded when there was a general relaxation of the duodenal musculature, although there was an actual increase of fluid in the lumen. Such a relaxation may occur when the loop of duodenum has become fatigued and after the administration of certain drugs. If the pressure in the common duct dropped below a varying minimal figure, there was not a discharge from the duct nor was there an increase of duodenal volume, even with vigorous peristalsis.

We have also, for the first time, recorded an alternate rise and fall of pressure in the common duct simultaneously with rhythmic or pendular movements of the duodenum (figure). These changes of pressure in the common duct, apparently due to rhythmic movements, are independent of the fall of pressure in the duct due to relaxation of tonus. The effect of the rhythmic movements on the common duct results in a second method of regulating the flow of bile. As these movements constrict the intramural portion of the duct, they may aid by acting as a pumping mechanism in the expulsion of bile from the duodenal



The upper tracing records tonus, movements and volume changes in the segment of duodenum between ligatures, *A*, distance of tracing above base line, representing the volume of fluid in the segment at the beginning of experiment, *B*, small wave, corresponding to a rhythmic contraction, *C* to *D*, large wave, representing a peristaltic movement, *E*, volume of fluid in segment of duodenum at end of experiment. Increase of volume over *A* should be noted. The lower tracing records pressure and volume changes in the common bile duct, *1*, small wave,

representing change of pressure in duct corresponding to *B*, a rhythmic contraction, *2*, at this point a pressure of 100 mm of physiologic sodium chloride solution in the duct was started. The fall in pressure is steplike, corresponding to a relaxation phase of a peristaltic movement. *3*, a constant pressure of 100 mm of physiologic sodium chloride solution was resumed. The fall in pressure from *2* to *3* represents the passage of 175 cc of physiologic sodium chloride solution from the common duct into the duodenum.

papilla The higher the pressure in the common duct, the more effective will be the emptying of the duct owing to relaxation of tonus of the duodenum and to rhythmic movements If the pressure in the duct is sufficiently high, it may overcome the tonicity of the duodenal wall so that the bile will enter the lumen without the aid of peristalsis or rhythmic movements

The evidence that the normal tonus of the duodenum is an important factor in the regulation of the flow of bile is substantiated by the use of drugs Varying quantities of 25 per cent and 50 per cent solutions of magnesium sulphate were introduced into the duodenal segment There was never a marked response to magnesium sulphate Peristaltic movements were not greatly increased and relaxation of the musculature was not great The fall of pressure in the common duct was correspondingly small

The injection of 1 or 2 cc of oleic acid into the duodenal segment caused a great increase of duodenal movements and fall of common duct pressure The relaxation of tonus of the duodenum was greatest approximately five minutes after introduction of the fatty acid Oleic acid produced a greater fall of pressure in the common duct than magnesium sulphate This effect of fats on the duodenum is probably one of the factors in the rapid emptying of the gallbladder after the ingestion of a meal of lipoids and fats as observed by Boyden⁵ and by Sosman, Whitaker and Edson⁶ The increased peristaltic activity and relaxation of tonus allow a part of the contents of the gallbladder to pass into the duodenum in the course of two hours

Intravenous injection of moderate doses of atropine sulphate permits a considerable reduction of pressure in the common duct It produces a decrease of tonus without greatly affecting the rate or amplitude of peristaltic movements It is possible, then, for the maximum discharge to take place from the duct during the relaxation phase of peristalsis

Epinephrine chloride also causes a relaxation of the intestine and a fall in the common duct pressure The fall is most marked during the rise of blood pressure from epinephrine

Intravenous injection of pituitary extract is followed by an initial immediate relaxation of the duodenum and a great fall in its common duct pressure corresponding to the rise of blood pressure The pituitary

⁵ Boyden, E A The Effect of Natural Food on the Distention of the Gallbladder, with a Note on the Change in Pattern of the Mucosa as It Passes from Distention to Collapse, *Anat Rec* **30** 333 (Aug) 1925

⁶ Sosman, M C, Whitaker, L R, and Edson, P J Clinical and Experimental Cholecystography, *Am J Roengenol* **14** 495 (Dec) 1925

extract, however, quickly increases the tonus and activity of the intestine. There may be a fall of pressure with each relaxation phase, such as occurs normally with peristalsis.

Pilocarpine and physostigmine increase the tonus of the intestine and thereby increase the amount of pressure that the duct will withstand. The increase of tonus is usually so great that in spite of increased movements of the duodenum there is no discharge from the common duct.

It is evident that drugs that affect the tonus of the duodenal musculature affect the discharge of bile from the common duct. There may be a discharge of fluid from the duodenal papilla with each relaxation phase of peristaltic movements in spite of an increase of tonus. The tonus may be so greatly increased, however, that there will not be a discharge from the duct during the relaxation phases of violent intestinal movements.

It was thought likely that tonus of the duodenum exerted the same regulatory control of the flow of pancreatic juice into the duodenum as the flow of bile. A similar method to that used in the preceding experiments was used in recording pressures in the pancreatic duct and changes in the duodenum. A large pancreatic duct in the dog opens into the duodenum a few centimeters below the duodenal papilla. It is comparatively short. The duct passes obliquely through the intestinal wall for a distance of from 0.5 to 1 cm.

There is considerable variation in the relationship of the pancreatic duct and the common bile duct in the human being. The relation in which both ducts enter the duodenum is variable. These variations have been studied by Mann.⁷ However, these variations do not alter the general anatomic arrangement of this region given by most textbooks of anatomy. The pancreatic duct of Wirsung in the human being, usually near its termination, comes in contact with the common bile duct, together with which it passes obliquely through the muscular coats of the intestine for a distance of about 1 to 2 cm and terminates in the ampulla of Vater, situated near the junction of the second and third portions of the duodenum.⁴ Hendrickson⁸ has shown the intimate relationship of the common bile duct, the duct of Wirsung and their investing muscular coats.

Tonus of the duodenum was found to exert the same regulatory control over the pancreatic duct as over the common bile duct. A fall of pressure in the pancreatic duct accompanies a relaxation of tonus. The same effect is obtained from drugs on the pressure in the pancreatic

⁷ Mann, F. C., and Giordano, A. S. The Bile Factor in Pancreatitis, *Arch Surg* 61 (Jan.) 1923.

⁸ Hendrickson, W. F. A Study of the Musculature of the Entire Extra-hepatic Biliary System, Including That of the Duodenal Portion of the Common Bile Duct and of the Sphincter, *Bull Johns Hopkins Hosp* 9 221, 1899.

duct as on the pressure in the bile duct. We do not have a record of changes of pressure in the pancreatic duct corresponding to rhythmic movements of the duodenum similar to those found in the common duct.

This regulation of the flow of bile and pancreatic juice that has been described offers an accurately timed mechanism for the efficient admixture of gastric chyme, bile and pancreatic juice. A relaxation period between peristaltic movements, during which time bile and pancreatic juice enter the duodenum, allows the chyme and secretions to be mixed together by rhythmic contractions. A peristaltic movement following a relaxation period sweeps this bolus of chyme and secretions down the intestine. The process is then ready to be repeated.

CONCLUSIONS

Tonus and peristalsis in the duodenum are of great importance in the regulation of the flow of bile into the duodenum. This control is independent of factors other than pressure of the bile in the common duct. The duodenal wall exerts a like control over the discharge of pancreatic juice from the pancreatic duct. Food, drugs and chemicals that affect tonus and peristalsis are factors in the regulation of the flow of bile and pancreatic juice into the duodenum.

DIRECT EXAMINATION OF THE GASTRIC JUICE

A NEW FUNCTIONAL TEST

ARNOLD GALAMBOS, M D

NEW YORK

For a study of gastric conditions we are able to avail ourselves of test meals, such as the Boas-Ewald, Riegel-Leube or Boas, which give a certain amount of evidence regarding both the motor and the secretory functions of the stomach. But if we are concerned with gastric motility alone, this can be examined more easily and accurately by roentgenographic methods, while in practice it has been demonstrated that the test meal method affords only partial information concerning irregularities in gastric secretion. In making use of the test meal we can only obtain a mixture of food and stomach secretions, never the pure gastric juice alone. And because of this dilution and chemical admixture with the ingested food, it is impossible to make any accurate estimate as to the precise amount of secretion given off, this difficulty being still further enhanced by the fact of its fractional withdrawal.

Normally, the outpouring of gastric secretion takes place only when stimulated by the ingestion of food, and examination of this secretion has been undertaken when it had previously been induced by the administration of the test meal. The original Ewald and Leube tests emptied the stomach at the height of digestion. Examination of the secretion from the fasting stomach was not undertaken except in suspected states of retention or hypersecretion.

DIRECT EXAMINATION OF THE GASTRIC JUICE

With the advent of the Rehfuß tube, however, we have a means that enables us to make examination of the gastric content by a fractional method, and it becomes possible to make routine study of the fasting stomach, investigating the gastric juice—its secretion, concentration and amount, as well as its influence, psychic and otherwise—very much as may be done in animal experimentation by means of fistulas or the Pawlow pouch.

TECHNIC

The Rehfuß tube is introduced into the fasting stomach, and its content withdrawn by means of a perfectly tight syringe. The tube is then left in place. As the gastric juice accumulates it is withdrawn at predetermined intervals—three, five, ten or fifteen minutes—and the quantity and total acidity of each portion separately determined. Any special examination, microscopic or otherwise, can be performed at the same time on any or all of these samples.

So far as my examination of the literature has gone, no such test has heretofore been recommended, either to complete the functional food tests in common use, or as a substitute for them, when it is desirable to obtain pure gastric secretion, unadulterated by food, a procedure which, as has been pointed out by Compton, would open up a wide field of study in relation to gastric function.

When the Rehfuß tube remains in the stomach the presence of its tip will excite and maintain the process of gastric secretion in those persons whose stomachs are in a state of hyperexcitability, in normal stomachs this mechanical stimulus will produce no secretion whatever. The observations reported in this article were made during the last eight months on some fifty patients, in the majority of whom there was a condition of gastric hypersecretion. Some 200 separate examinations of the fasting stomach content were made on these patients, the single determinations on the withdrawn samples numbering more than 1,000.

These cases can be roughly divided into two groups: (1) those in which no hypersecretion exists, in these there is no free gastric juice—or at most from 5 to 10 cc. of mucus showing hypacidity—and there is no drainage from the tube, no matter how long it is left in place, its tip failing to stimulate the secretory mechanism of the fasting stomach, (2) those in which hypersecretion is present. In these the introduction of the tube produces an outpouring of gastric secretion when the stomach has received no food for an extended period. Examination should be carried out after an alimentary rest of from twelve to fourteen hours, preferably in the early morning. The patients in this group comprise those suffering not only from primary hyperacidity or hypersecretion, but also from peptic ulcer of the stomach or duodenum, hypersecretion with anacidity, and all other diseases that are accompanied by secondary disturbances of gastric secretion. As to the incidence of gastric hypersecretion, I may quote the statement of Einhorn: "In varying conditions other than gastroduodenal ulcers, perhaps nine out of ten exhibit signs of this secretory anomaly," although this estimate seems to me somewhat high.

SIGNIFICANCE OF SECRETORY DISORDERS

The significance of acidity of the gastric juice, or of the gastric content as a whole, may be evaluated from different points of view. Though anacidity or achylia is one of the most significant indications of gastric cancer, we know that it may be encountered in other morbid conditions, not only of the stomach but elsewhere in the organism, or even under normal conditions. When peptic ulcer exists hyperacidity and hypersecretion may accompany it, but, again, both these manifestations may be entirely lacking with peptic ulcer while, on the other hand, they may appear in connection with other morbid conditions or even be

present in otherwise normal health. In the normal person, too, there is often a wide divergence in the character of the stomach secretions obtained on different occasions, and this is even more true of persons out of health from any cause whatsoever. Therefore, there are no secretory findings absolutely pathognostic of any disease. If we take all these considerations into account it would hardly seem worth while to undertake any examination of the gastric juice, as the interpretation of the findings is subject to so many limitations. I say seem, for these limitations have been well characterized by Rehfuess and Hawk,¹ when they say, "Let us realize here and now with gastric analysis, as with X-ray, that neither lies, but it is our interpretation which is faulty." Our interpretation has been faulty in the past, but not lately, because we have

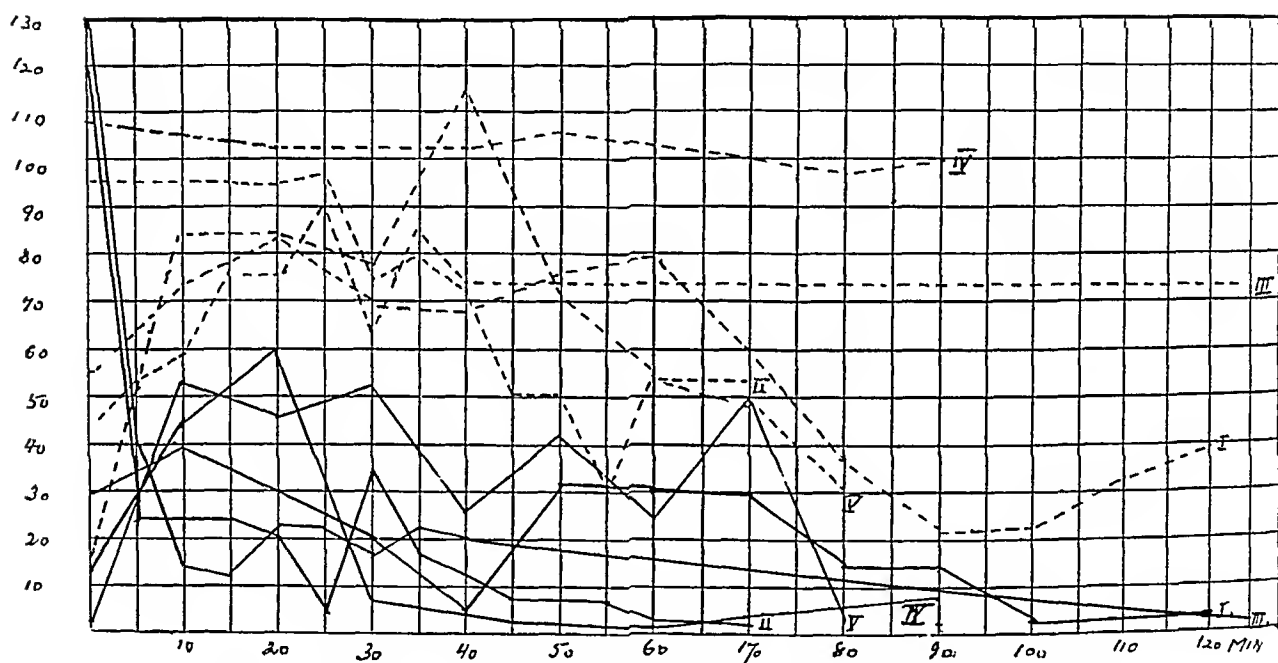


Chart 1—Gastric juice on fasting and after aspiration in five minute intervals. Functional test at five different times, at about two day intervals, in B. R., a man, aged 56, with ulcer of the duodenum of twenty years' duration, with severe recurrences. Broken line total acidity, solid line gastric juice (cubic centimeters).

never obtained the gastric juice in unadulterated form, if we can now obtain the secretion in such a form that we are able to interpret it correctly, it certainly seems well worth while to undertake the labor involved in making accurate analyses.

The need for such study is at once apparent when we consider the wide divergence of opinion regarding all aspects of gastric analysis.

¹ Rehfuess, M. E., and Hawk, P. B. A Consideration of the Gastric Test Meal from Experimental Data, Tr. Twenty-third Ann. Meeting Am. Gastro-Enterol. A., May 3-4, 1920.

Earlier investigators asserted that between meals the stomach remained empty or at the most contained but a few cubic centimeters of clear gastric juice, showing perhaps a slight acidity. Rehfuess and Hawk, on the other hand, consider as an average normal finding in the fasting stomach about 50 cc of fluid with free hydrochloric acid and a total acidity of from 30 to 50. My own experience is in accord with the earlier observations. Again, hypersecretion is generally cited as an almost pathognomonic sign of ulcer in the stomach or duodenum, yet Einhorn, in a number of conditions other than peptic ulcer found hypersecretion in 90 per cent. When no basic principles uniformly stated and accepted exist, how can we hope to establish any sound or practical clinical procedure?

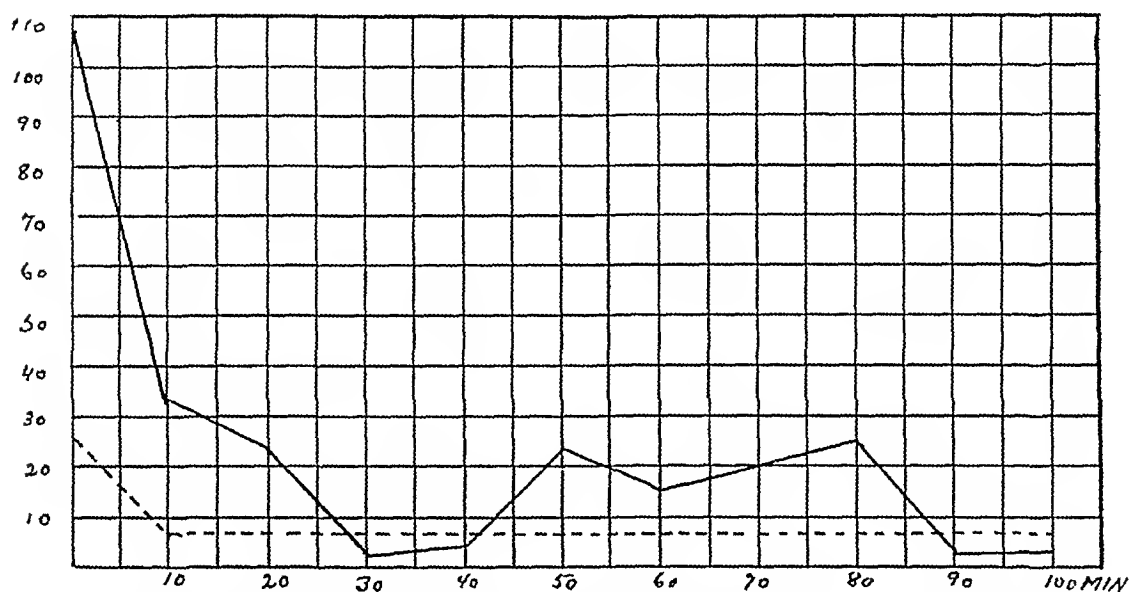


Chart 2—Gastric juice on fasting and after ten minute intervals in H S, a man, aged 54, with a tentative diagnosis of carcinoma ventriculi, hypersecretion and anacidity. Symptoms had been present for the last six years, and had been worse for the last six months. Free hydrochloric acid on fasting was 8, later it was always missing. Broken line total acidity, solid line gastric juice (cubic centimeters).

Some time before I elaborated this procedure, another method was adopted by Garbat,² while engaged in experimental work in Jacob Kaufman's service. After instituting duodenal alimentation, he observed an outpouring of gastric secretion analogous to that set up by the entry of food into the stomach, the secretion remaining in the stomach so long as there was any food in the duodenum. In other words, a definite cycle of gastric secretion took place, which was characteristic of

2 Garbat, A. L. Gastric Secretion in Response to Duodenal Feeding, *Arch Int Med* **32** 771-778 (Nov) 1923, A New Method for Studying Pure Gastric Secretion, *Am J M Sc* **169** 687 (May) 1925, Treatment of Gastric Ulcer by the Method of Duodenal Alimentation, *J A M A* **84** 1992-1994 (June 27) 1925

the individual's peculiar make-up, as has been especially emphasized by Kaufman, even when no food actually entered the stomach cavity or as I have been able to demonstrate, when the stimulus to outpouring of secretion was due to the presence of the tube in the stomach. Rehfuess thought the material of which the tip was made, whether metal or rubber, was of importance, but Einhorn has pointed out that this is of no significance. It is certain that the tube does not induce the secretion. It merely increases its amount and maintains it, because in these cases of hypersecretion, the process is continuous and spontaneous.

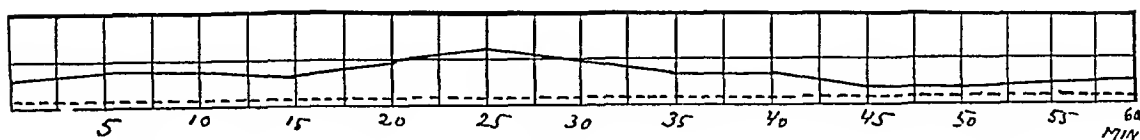


Chart 3—Gastric juice on fasting and after aspiration in five minute intervals in S K, a woman, aged 26, with gastric neurosis. All samples showed anacidity, the gastric juice was of thick, glassy, mucous quality. Broken line total acidity, solid line gastric juice (cubic centimeters).

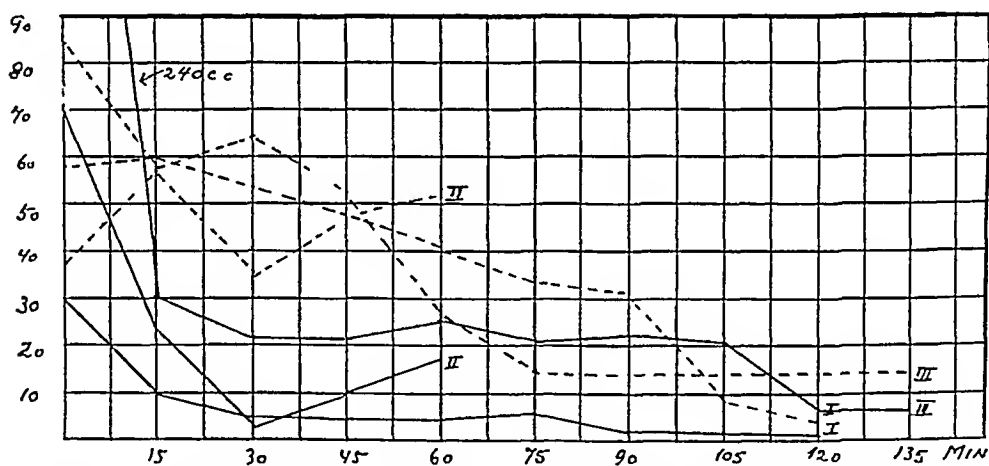


Chart 4—Gastric juice on fasting and after aspiration in fifteen minute intervals in F H, a woman, aged 34, with a moderately severe case of duodenal ulcer. Two parallel tests were performed at a one day interval. In the third, a tube was inserted two hours after a Ewald-Boas test breakfast, the first four portions withdrawn still contained residual meal, all the other samples were clear gastric juice. Broken line total acidity, solid line gastric juice (cubic centimeters).

While both Garbat's method and my own provide for obtaining unadulterated gastric juice for analysis or other purposes, and I have no wish to minimize or deny the scientific value of Garbat's method, I still feel that my own is worthy of greater consideration, if for no other reason than its extremely easy application, its performance being even more simple than the administration and examination of a test breakfast.

PECULIARITIES OF SECRETED GASTRIC JUICE

While it is evident that it will not be possible to withdraw all the gastric juice entering the stomach, as some is bound to escape through the pylorus, we must not make too great an allowance for such discrepancies, and there is no doubt that the quantity withdrawn gives an excellent approximation to the amount actually secreted

If the tube introduced into the fasting stomach does not produce any secretion it is not likely to do so if allowed to remain in place. If the stomach contains free gastric juice, the tube will give a more or less continuous return, this being to some extent proportional to the quantity and concentration of the gastric juice which was present in the fasting stomach. If there is any irritative secretory disturbance in the viscus under examination, the tube left in place will after a few minutes show the start of a typical secretion curve, and this curve will be more characteristic and convincing than were the observations made when the fasting stomach was first entered.

Usually the quantity and concentration of the gastric juice will be greatest some five or ten minutes after the introduction of the tube. When the mechanism of secretion has been at work for some thirty to forty minutes there will be a noticeable decrease in the amount out-poured, this is an expression of exhaustion. Decrease in concentration and in quantity may occur simultaneously, or follow one after the other, but the curve always shows marked individual variation, and even in the same subject under identical conditions, there may be differences all the way to 100 per cent in acidity values, and even more than 100 per cent in the quantity of gastric juice secreted. During the phase of exhaustion, the material withdrawn may contain mucus or duodenal secretion, with a visible admixture of regurgitated bile. As a rule, this depressed or inhibited phase will last from five to fifteen minutes, after which the process of secretion will be resumed at approximately the previous rate. After the lapse of thirty to sixty minutes, another longer and more lasting phase of exhaustion will set in, this sometimes continues for many hours. During the night's rest gastric secretion is relatively inhibited, so that often the amount found in the stomach in the morning will be relatively much less than one would expect to find in correspondence to the height of secretion during the test. It is understandable also that the secretion curve should drop after being exaggerated by stimulation, for otherwise there would quickly be an imbalance in the chemical reaction of blood and tissues, a rapid exhaustion of the system and an enormous alkalosis of the blood which would be incompatible with life.

For example, in a severe case of hypersecretion due to chronic duodenal ulcer, 170 cc of gastric juice was obtained from the fasting

stomach, at three minutes intervals, with a total acidity of 80, the average amount withdrawn at one time being 30 cc. Thus, in the first half-hour there was a loss of 300 cc of gastric juice, with a concentration of 80. Had secretion continued at this level for twenty-four hours, there would have been a loss of 15 liters of gastric juice, which would have entailed total dechlorination of the system.

The ingestion of food acts as a chemical stimulus to increased secretion, and also as a source of further secretion. This irritative secretory condition is responsible for a more or less continuous process often enduring for weeks or even months, during which relief is only afforded by incessant or recurring vomiting. As the food intake is deficient in spices, especially in salt, it is obvious that such a high degree of hypersecretion could not possibly persist for any length of time.

OBJECTIONS TO THERAPEUTIC DUODENAL FEEDING

Duodenal feeding has recently attained much popularity as a means of resting the stomach or duodenum when ulcer is present. I feel however, that the difficulty of keeping the duodenal tube in place for the long period of time necessary is a very serious drawback to this procedure, and agree with Arthur L. Holland when he says: "Notwithstanding the many favorable reports of duodenal feeding, I believe that the principle is wrong, that whatever is gained in resting of the secretory apparatus of the stomach is lost in the spasm and irritation the tube must constantly excite." In addition to the loss of gastric digestion and the psychic reaction which attach to this method and are mentioned by Holland, I would point out the loss of the food's acid binding power—peculiarly true of proteins—which is so advantageously employed in Lenhartz's diet. All these are factors mitigating against the employment of duodenal feeding.

Should this method of alimentation be adopted, not only is the acid binding power of the proteins lost, but also—and notwithstanding the general views based on the results of this test—the secretory apparatus instead of being put at rest is kept in a hyperactive state, temporarily at least, except during the phase of exhaustion. It may be objected that in duodenal alimentation the tip of the tube is in the duodenum, while in the method I am advocating, the tip does not pass through the pylorus. In answer to this in addition to the mechanical insult of the tube on the gastric mucosa I may cite the experiments of Garbat already quoted that irritation in the duodenum and frequent gastric regurgitation are the threefold reason causing the mechanism of stomach secretion to become active, so that actually the stomach does not "rest" even when no food enters it.

Whatever the interrelationship between hyperacidity or hypersecretion and peptic ulcer may be, it is certain that their coincidence is not

merely accidental. It is rather a fairly regular condition and the wonderful results obtained following subtotal gastrectomy, when the hydrochloric acid disappears and there is no recurrence of ulceration, as Berg³ has so especially emphasized, prove that the relationship between these pathologic conditions is a close one. If the gastric mucosa is kept in a condition of irritation by the permanent presence of the duodenal tube, thereby provoking and increasing gastric secretion, it is evident that it will favor the development and persistence of gastric ulcer, rather than aid in abolishing it. There has been practically no contradiction of the results reported from the studies of Portis and Portis,⁴ wherein it was shown that "neutralization plays the most important rôle in explaining the absence of free hydrochloric acid, observed experimentally and clinically in the gastric secretion after subtotal gastrectomy," and this is because the absence of free hydrochloric acid is associated with high combined acidity.

CONCLUSIONS

1 The Rehfuß tube may be introduced into the fasting stomach and left there to induce gastric secretion, which can then be fractionally withdrawn.

2 The examination and study of gastric juice unmixed with food can thus be made possible, and the results used to complete the test meal examinations, or as a substitute for them as the method gives a more exact account of the concentration and quantity of gastric juice secreted.

3 Two types of gastric secretion are discriminated, that of the normal stomach and that of the stomach affected with irritative secretory disturbance.

4 In the normal stomach after fasting, even when the tube is left in place from ten to sixty or more minutes after introduction, no gastric secretion can be obtained, either by drainage or suction.

5 In the stomach affected by irritative secretory disturbance, there is hypersecretion on fasting, usually with hyperacidity, though normal acidity and occasionally anacidity may be noted. After a three to fifteen minute interval similar gastric juice may be obtained by suction. Occasionally, hypersecretion with anacidity is found in cases showing free hydrochloric acid and possibly later hyperacidity after the customary test meals.

6 The amount of gastric juice secreted immediately after the insertion of the tube may be several times greater than the *relative* quantity

3 Berg, A. A. Radical Cure of the Gastric and Duodenal Ulcer, read at the New York Academy of Medicine before the American-Hungarian Medical Association, Feb. 16, 1926.

4 Portis, S. A., and Portis, Bernard. Effects of Subtotal Gastrectomy on Secretion, J. A. M. A. 86:836 (March 20) 1926.

accumulated during the night's rest The acid concentration is, as a rule, much less increased

7 From one-half an hour to one hour after the tube is inserted, a phase of exhaustion of the mechanism of gastric secretion will intervene, the quantity and concentration of the gastric juice being temporarily markedly reduced

8 This phase of exhaustion is characterized by a protective mechanism which produces a secretion with heavy admixture of mucus and regurgitated gall, and also containing duodenal secretion

9 The first phase of exhaustion endures from ten to fifteen minutes After an active interval of thirty to sixty minutes, there will be a second period of exhaustion, often lasting many hours

10 Information concerning the motility of the stomach can be obtained through the use of this test, at the same time the gastric juice is being withdrawn for study For this purpose it should be performed when the stomach has just been emptied after the administration of a test meal, e g , two hours after the test breakfast

CAPILLARY PERMEABILITY AND THE INFLAMMATORY INDEX OF THE SKIN IN THE NORMAL PERSON AS DETERMINED BY THE BLISTER *

WILLIAM F PETERSEN, M D

AND

DAVID A WILLIS, M D

CHICAGO

In the recent advances made in the study of the capillaries, methods of visualization have played the larger rôle, with the result that most investigators have studied alterations in appearance rather than function, and if the latter, only indirectly. Much of the work has taken origin in the careful work of Otfried Muller¹ and of Krogh². Stricker,³ Hooker⁴ and Ebbecke⁵ have devoted much time to a study of the functional alteration of the capillary and Ebbecke particularly to the bio-electrical changes that accompany or initiate changes in function. Ebbecke's work can be correlated with the clinicopathologic studies of the Kraus⁶ school on the ionic equilibrium of the body, particularly the calcium and potassium balance.

We have heretofore been accustomed to think of the capillary system and its functional control in terms of the vasomotor nervous mechanism and have come to confuse the reaction of the musculature of the arteriole with the presumptive reaction of the capillary wall. Indeed, an independent dilatation and contraction of the capillary has until recently been regarded as improbable, or merely of academic interest.

The single endothelial cell (disregarding for the moment any adventitial element, such as the Rouget cell) of the capillary wall has the inherent protoplasmic reactivity of any other cell. Its surface membrane is the seat of the same bio-electrical, ionic and physical changes that accompany changes in reactivity in a free living ameboid cell. Stimulation involves lessened turgor, lowered surface tension, greater permeability, lowered surface charge, lessened calcium and increased

* From the department of pathology, University of Illinois College of Medicine

1 Muller, Otfried. *Die Kapillaren der menschlichen Körperoberfläche*, Stuttgart, 1923

2 Krogh, August. *Anatomy and Physiology of the Capillaries*, Yale University Press, 1922

3 Stricker. *Vorlesungen über die allgemeine und experimentelle Pathologie*, Vienna, 1883

4 Hooker, D R. *Physiol Rev* **1** 112 (Jan) 1921

5 Ebbecke, U. *Klin Wchnschr* **2** 1725 (Sept 17) 1925

6 Kraus, F, and Zondek, S G. *Klin Wchnschr* **1** 996 (May 13), 1922 (Sept 2) 1922. Zondek, S G. *Ibid* **4** 905 (May 7) 1925

potassium content And with endothelium making up a hollow tube, stimulation will result in the capillary becoming more distensible and the lumen larger

Such a change may be brought about by a nerve impulse—and the demonstration of nerve fibers to the capillary walls seems well established—but more likely it is due to direct effects on the cell surfaces by alterations in the blood plasma, or of the tissues of the region supplied by the capillary Fundamentally such changes are, of course, ionic and bio-electrical, i e, changes in the hydrogen ion concentration and in the calcium-potassium balance

Alterations brought about by nerve impulses or as the result of hormone changes are also brought about by ionic rearrangement It has been repeatedly demonstrated that the nerve impulse will elicit a response depending in its character on the ionic equilibrium obtaining at the time the impulse reaches the cell Experiments have been reported which show that the effect of the hormones likewise depends in a large measure on the ionic equilibrium existing at the cell surface

Evidence can be cited at length from the work of Lillie, Osterhaut, Embden and Gildermeister, to mention only a few, that the cell can respond to an alteration of external conditions in one of two ways The cell membrane may become *more permeable* (we usually think of this modification of the state of the cell as stimulation) and accompanying this change will have enhanced oxidation, increased excretion of lactic acid, phosphates and calcium, it will take up more potassium, the surface charge will be lessened, the surface tension reduced, the cell turgor lessened, ameboid motion and phagocytosis will be enhanced It may become *less permeable* (we regard this in specialized cells as a refractory period, in a general sense as a period of rest), will contain more calcium and less potassium, will have a higher surface potential, with greater surface tension, greater turgor and less ameboid motion Either change may take place as a reaction to environmental alterations and in this sense we may regard the effect of a stimulus as one that will increase or retard activity of the cell This is perhaps contrary to the usual physiologic or pathologic concept, and yet we believe on analysis will be found to be logical

If we now examine the factors that, when acting directly, alter the cell in one direction or the other we find approximately those given in table 1

Our endothelial cell may respond to any of these agents, becoming either more or less permeable as the case may be Largely it will be a local control as a result of environmental changes of the surrounding tissue But it may be hormonal and in some instances autonomic, always bearing in mind that many of the autonomic agents also act directly on the endothelial cell itself, without reference to neurocellular junction

Let us examine for a moment the contractile mechanism. That at best is rudimentary and incomplete. The Rouget cell is relatively undifferentiated—pathologists frequently group the tissue with reticulothelium (Marchand). These cells seem definitely under autonomic control, contracting on stimulation of the local sympathetics and with epinephrine application. They correspond in general to the innervation of the arterioles.

This muscular mechanism has been superimposed on the more primitive system and its nervous control, too, is a later addition to the mechanism of regulation. Consequently direct stimulation of the endothelium (with increased permeability and dilatation of the capillary) may occur simultaneously with stimulation of the musculature through a nervous influence, so that we will have effects which in many respects are seemingly antagonistic. Usually, however, the capillary becomes permeable with agents that act on the parasympathetic system and so cause capillary dilatation and increased permeability as well as arteriole relaxation.

TABLE 1—*Factors That Alter Cell*

Increased Permeability	Diminished Permeability
1 Parathyroid, thyroid (?), sex hormone (menstruation)	1 Epinephrine, pituitary extract, insulin (?)
2 Pilocarpine, muscarine, choline, peptone, paraphenyldiamine, physostigmine, etc	2 Picrotoxin, strychnine, santonin (because of mobilization of epinephrine)
3 Caffeine, theophylline, etc	
4 Many of the narcotics, including alcohol, veronal, etc	3 Diminished hydrogen ion concentration
5 Increased hydrogen ion concentration	4 Diminished temperature
6 Increased temperature	5 Calcium effects
7 Potassium effects	

In previous articles⁷ we have studied capillary permeability in the experimental animal by means of thoracic duct incannulation. These studies showed the relatively rapid reversibility of membrane changes—period of time by a reversal to impermeability—with later further fluctuations. We were able to demonstrate the increase in permeability in shock from peptone and anaphylaxis, as a result of the primary effect of tuberculin and of arsenic, and the decrease in permeability with epinephrine and pituitary extract and as a secondary phenomenon following tuberculin and arsenic. We then studied the chemical changes in the lymph that accompany these alterations. The relation to the autonomic nervous system has been discussed by Muller and one of us.⁸ It seemed desirable to us to examine the permeability of capillaries of normal persons as well as under various pathologic conditions, and in

⁷ Petersen, W. F., Levinson, S. A., and Hughes, T. P. *J. Immunol.* **8**: 323 (Sept.) 1923.

⁸ Muller and Petersen. *Klin. Wchnschr.* **5**: 2, 1926.

considering the possible methods for such a study we finally have adopted the simple expedient of making a cantharides blister and determining the ratio of protein that comes through into the blister as compared to the protein concentration of the serum

Blister formation in patients has been used by a number of investigators in biochemical or serologic problems. As far as we can determine the only one who has worked with the blister method for the purpose that we have in view has been Gannslen.⁹ Otfried Muller and his associates have been interested chiefly in the microscopic study of the capillary in the living subject and in order to obtain some information as

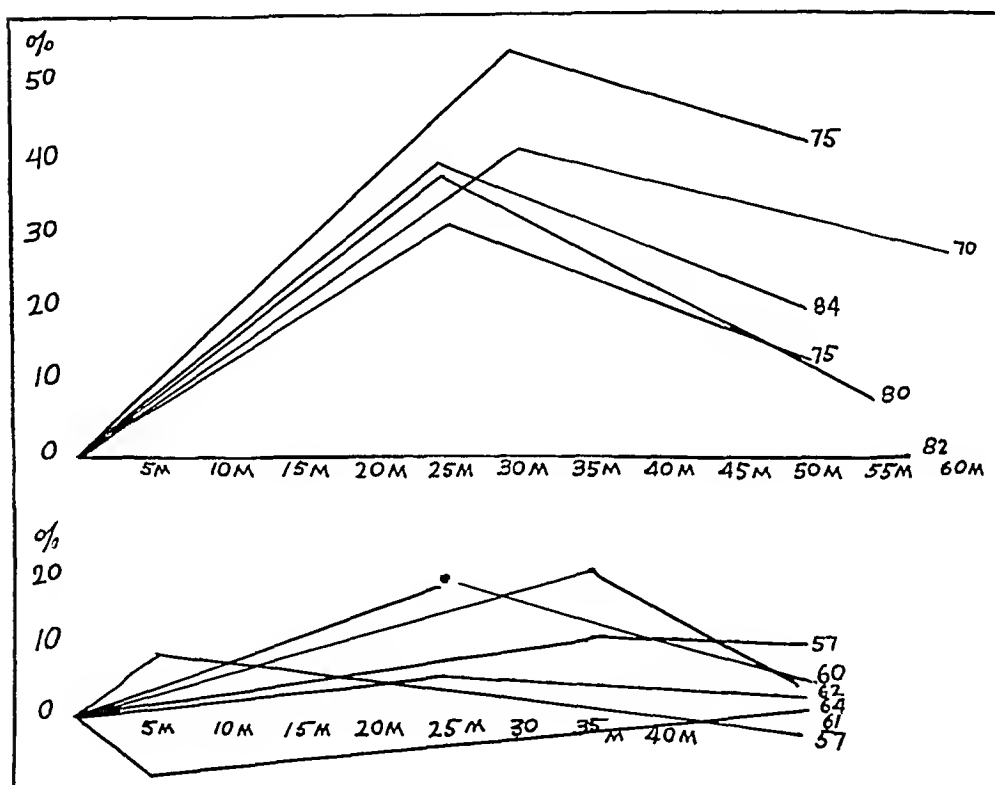


Chart 1—Effect of 5 minims of epinephrine (1:1,000) subcutaneously, expressed as pulse rate times pressure in percentage of normal, upper group 1, permeable, lower group 2, impermeable

to the functional capacity, Muller suggested the possibility that the blister might be of use. Gannslen used cantharides plaster applied to the outer surface of the ankle. He placed six small plasters on the skin and he had them removed at intervals of two hours. On observing the blister formation the following day he would note the length of time that it had required for the plaster to draw a blister, and this was then noted as the blister time. With his plaster and method, the average normal time was

⁹ Gannslen, M., and Muller, O. *Munchen med Wchnschr* **69** 263 (Feb 24) 1922. Gannslen, M. *Ibid* **69** 1176 (Aug 11) 1922.

approximately twelve hours. Much shortening was noted in the vascular neuroses, in exophthalmic goiter, and in severe diseases associated with hemorrhagic diathesis. He determined the amount of protein in some of the blisters but made no systematic study of permeability, although Muller in his introduction mentions the desirability of such investigation. Gannslen later studied the relative amount of nonprotein nitrogen and sugar in the blister fluid and serum in cases of nephritis.¹⁰

The dermatologists have studied blister formation and Weidenfels¹¹ in particular has devoted much attention to the subject. He concludes that the fluid is drawn from the lymph spaces. Whether from lymph spaces or directly through capillary wall is, however, for the purpose that we have in mind, immaterial. In either instance the fluid must have

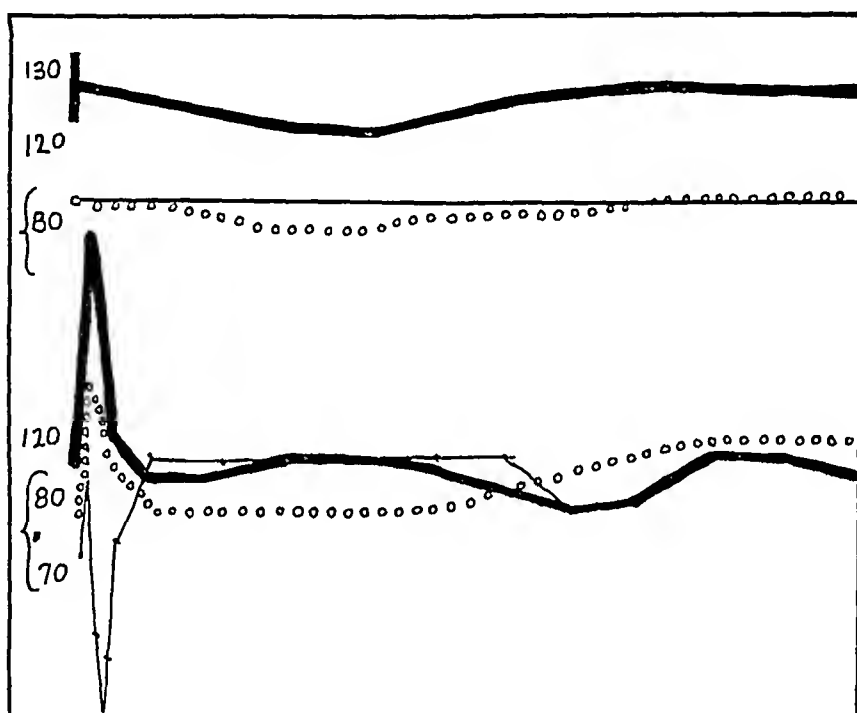


Chart 2—Upper effect of 5 minims of epinephrine subcutaneously on student 12, ratio, 61, lower effect of 1 minim of epinephrine intravenously, heavy line, systolic, dotted line, diastolic blood pressure, light line, pulse rate

passed through an endothelial wall and have been modified in its protein concentration by so doing. Gannslen noted that it was immaterial by what means the blister was produced and regarded the cantharides plaster as the most useful. Cantharides being lipid soluble enters the skin readily and probably produces its effect in two ways, on the sensory nerve ending and directly on the capillary wall.

The stimulation of the sensory nerve ending apparently is transmitted directly as an axone reflex to the adjacent skin arteriole, for it has been

¹⁰ Gannslen, M. *Munchen med Wchnschr* **70** 1271 (Oct 12) 1921

¹¹ Weidenfels, quoted by Pulay. *Eczem und Urticaria*, Vienna, 1925

repeatedly demonstrated that such reflexes may take place with total severance from the central nervous system (Bayless, Bruce, Spiess) and Bruce¹² has furthermore shown that when the sensory ending is anesthetized, inflammatory agents that act solely through the nervous pathway are no longer able to induce inflammation

Cantharides acts also as a specific capillary irritant without altering the rest of the protoplasmic elements to any great extent. It is this property that causes it to produce an inflammatory reaction even when the sensory effects are blocked

METHOD

Blister Time—We have used a common commercial grade of cantharides plaster (B and B). This has been applied at a definite time (4 a. m. for patients, 8 a. m. for student controls) in the morning, the plaster left on for six hours, then removed and the area observed at

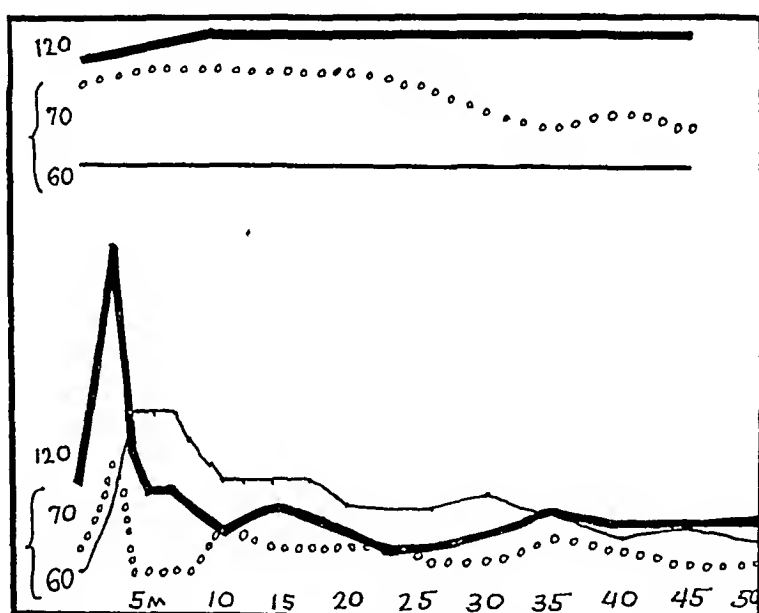


Chart 3—Upper effect of 5 minims of epinephrine subcutaneously on student 65, ratio, 82, lower effect of 4 minims of epinephrine intravenously, heavy line, systolic, dotted line, diastolic blood pressure, light line, pulse rate, \uparrow , time of injection

intervals for blister formation. The time when the first definite elevation appears has been taken as the blister time. In some patients the blister time is very short. A severe burning sensation usually brings the plaster to the attention of the patient and in these cases the plaster has usually been removed at an earlier time.

The plaster has been uniformly applied to the inner surface of the forearm just below the elbow.

Permeability Ratio—Sufficient fluid having collected, the blister is immediately evacuated (if fluid remains for any length of time in the blister, its protein content diminishes, probably because of proteolysis) and at the same time a blood sample is collected in a Wright capsule from the ear lobe. Disregarding fibrin, the two samples (blister fluid and serum) are now examined by means of the refractometer for their protein content. The readings for the blister fluid are made according to the Reiss exudate table, those for the serum from the regular serum table. The ratio $\frac{\text{percentage of blister protein}}{\text{percentage of serum protein}}$ gives us our permeability ratio.

Inflammatory Index—If we now wish to express the relative inflammatory response of the individual to the particular irritant in question we use the following coefficient $\frac{\text{permeability ratio}}{\text{blister time}}$. For example, blister protein is determined as 4 per cent, the serum protein as 6 per cent. The permeability ratio is 66. It takes eight hours to form the blister. $\frac{66}{8} = 8.2 = \text{inflammatory index}$.

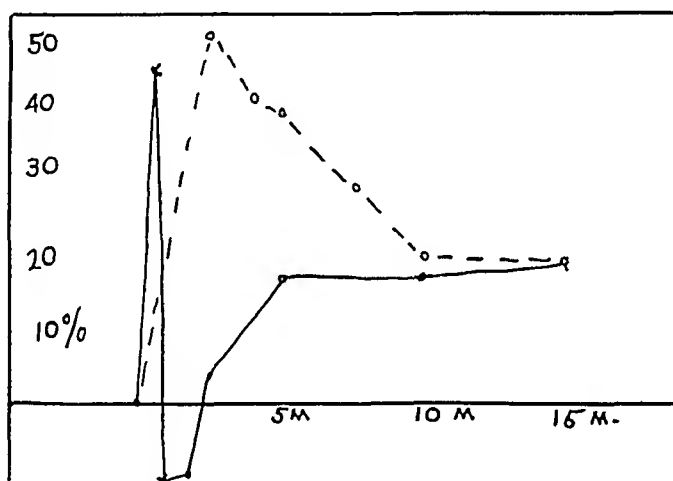


Chart 4—Solid line effect of 1 minim of 1:1,000 epinephrine on student 12, broken line effect of 4 minims of 1:1,000 epinephrine on student 65, in terms of pulse rate times systolic pressure in percentage of increase from normal before intravenous injection.

We need not emphasize that it is essential to work under uniform conditions. Repeated control observations in the same persons under such circumstances have given us quite comparable results, the variation being from 2 to 4 per cent. It is essential, however, that a uniform plaster be employed.

These two coefficients give us direct information about two more or less distinct phenomena. The index of permeability indicates the *actual degree of response of the capillary endothelium to a direct stimulus* (in this case the cantharides). It has no direct relation to the autonomic nervous system except so far as the underlying endocrine and ionic equilibrium affect both protoplasm and autonomic nervous tissue.

The inflammatory index includes the effect of the autonomic tonus. If a blister forms rapidly we have every reason to believe that the axone reflex has produced a prompt relaxation of the arteriole musculature because the tonus of the sympathetic system is low, conversely, the delayed blister indicates that the relative sympathetic tonus is high and that the spasm of the arteriole musculature is the factor that delays the transudation of fluid from a capillary that may be relatively permeable. Usually increase in capillary permeability goes hand in hand with diminution of the sympathetic tonus, but not always¹³

Normal Men—Before proceeding to a study of patients we have taken advantage of the opportunity of studying normal young men and women, for which purpose we have had the voluntary cooperation of some seventy students.

We have examined, in addition to their blister time and permeability, the following in all or in smaller groups of students: Urine, blood pressure, blood chemistry, basal metabolic rate, the epinephrine reaction, the reaction to roentgen rays, and the tuberculin reaction. In addition we obtained a history of the student and a roentgenogram of the thorax.

The following presentation details the relation of some of these observations to the relative permeability and inflammatory reaction of a group of sixty-six of such students (men in the age group of 22-25). In table 2 the material has been grouped in the order of the relative permeability of the students, in table 3, in the order of the inflammatory index.

As shown in the second table, the permeability varies from 57 to 84, and the table has been divided into two portions, *A*, low permeability, *B*, high permeability. The average for the whole group is 68, which has been used as the dividing line.

The inflammatory index varies from 3.5 to 18.5, the average for the entire group being 10.5. This table also has been divided into two groups, with thirty-four students in the first group and thirty-two in the second (to correspond to the first table).

ANALYSIS OF RESULTS

Clinical Examination—Presumably the students were all normal. On examination it will be seen, however, that there were several exceptions.

Students 32 and 34 were found on roentgen-ray examination to have evidences of active tuberculosis. The lesion in student 32 was associated with obvious constitutional effects.

¹³ We have stressed the tonus of the arteriole in producing a long or short blister time and in relation to the inflammatory index merely for the sake of simplicity. The subject is, of course, much more complex and it might indeed be more proper to speak of the tonus of the whole tissue. Landner many years ago studied just such a relation of the connective tissue elements to the formation of an edema.

TABLE 2—*Normal Student Group Arranged According in Relative Capillary Permeability*

A								
No	Permeability Ratio	Clinical Diagnosis	University Athletics	Sensitization	History of Clinical Tuberculosis	History of Family Tuberculosis	Roentgen-Ray Diagnosis	Urinary Changes
1	0.57	Psoriasis	—	—	—	—	—	—
2	0.57	—	—	—	—	Sister active	1 Ghon†, healed pulmonary	—
3	0.57	—	Yes	Hay-fever	—	—	Hilum	—
4	0.57	—	—	Urticaria	—	—	Hilum	—
5	0.57	—	Yes	—	—	Brother died	Hilum	—
6	0.57	—	—	—	—	—	Hilum	—
7	0.59	—	Yes	Horse serum	—	—	Hilum	—
8	0.59	—	—	—	Yes (kidney)	Entire family	2 Marked hilum shadows	—
9	0.60	—	—	—	—	?	3 Marked calcification of costal cartilages	Albumin and casts
10	0.60	—	—	—	—	—	Normal	—
11	0.61	—	Yes	—	—	—	Hilum some what increased	—
12	0.61	—	Yes	—	—	—	4 Old healed pulmonary	—
13	0.61	—	—	—	—	Grand-parents, uncle	Hilum	—
14	0.62	—	Yes	—	—	—	5 Old healed pulmonary	—
15	0.62	—	—	—	—	—	Normal	—
16	0.63	—	—	—	—	—	6 Old healed pulmonary	—
17	0.63	—	—	—	—	Father	7 Old healed pulmonary	—
18	0.63	—	—	—	Yes	—	8 Possibly old healed pulmonary	—
19	0.63	—	—	—	—	—	Hilum	—
20	0.63	—	Yes	—	—	—	Normal	—
21	0.64	—	—	—	—	—	Marked hilum	—
22	0.64	—	—	—	—	—	9 Old healed pulmonary	—
23	0.64	—	Yes	—	—	Yes	Normal	—
24	0.65	—	—	—	—	—	Increased hilum shadows	—
25	0.65	—	—	Horse serum	—	—	Normal	—
26	0.65	—	—	—	—	—	Normal	—
27	0.65	(During migraine)	—	—	?	Yes	Hilum	Albumin and casts
28	0.65	—	—	—	—	—	Hilum	—
29	0.65	—	—	—	—	—	Hilum	—
30	0.66	—	Yes	—	Yes	Brother	10 Old healed pulmonary	Occasional casts
31	0.66	—	—	—	—	—	Normal	—
32	0.66	—	—	—	—	Uncle	11 Active right upper lobe	—
33	0.67	—	—	—	—	—	Hilum	—
34	0.67	—	—	—	—	—	12 Active right upper lobe	—
			9	4	3	9	12	3

† Ghon tubercle—a healed primary lesion of the lung

TABLE 2—Normal Student Group Arranged According to Relative Capillary Permeability (Continued)

B								
No	Permeability Ratio	Clinical Diagnosis	University Athletics	Sensitization	History of Clinical Tuberculosis	History of Family Tuberculosis	Röntgen Ray Diagnosis	Urinary Changes
35	0.68	—	—	—	—	—	Hilum	
36	0.68	—	—	—	—	—	Hilum	Albumin and casts
37	0.68	—	—	—	—	Yes	Hilum	
38	0.69	—	—	—	—	—	Hilum	
39	0.70	—	—	—	Once suspected	—	1 Ghon, left lobe	Albumin (faint trace)
40	0.70	—	Yes	—	—	—	Hilum	
41	0.70	—	—	—	—	—	Normal	
42	0.70	—	—	—	—	Yes	Normal	
43	0.70	—	—	—	—	—	Marked hilum	
44	0.70	—	—	—	Yes	—	2 Healed upper right pulmonary	
45	0.71	—	—	—	—	—	3 Ghon, left lobe, healed upper lobe, pulmonary	Albumin
46	0.72	—	—	—	—	—	Hilum	
47	0.72	—	—	—	—	—	Hilum	
48	0.72	—	—	—	—	—	Marked hilum, healed parenchyma (?)	
49	0.73	—	—	—	—	—	Moderate hilum	
50	0.73	—	—	—	—	—	Hilum	Occasional casts
51	0.73	—	—	—	—	—	Hilum	
52	0.74	—	—	—	—	—	Hilum	
53	0.74	—	—	—	—	—	Hilum	
54	0.74	—	—	Yes	—	—	Old adhesions, pleurisy (not tuberculous)	
55	0.74	Congenital ichthyosis (mild)	—	—	—	—	Hilum	
56	0.74	—	—	—	—	—	Marked hilum	
57	0.74	—	—	—	—	—	4 Old healed pulmonary	
58	0.75	—	—	—	—	—	Moderate hilum	
59	0.75	Duodenal ulcer	—	—	Glands of neck in childhood	—	5 Ghon, moderate hilum	
60	0.76	—	—	—	—	—	Normal	
61	0.77	—	—	—	—	—	Hilum	
62	0.77	—	—	—	—	—	Hilum	Albumin and casts
63	0.79	—	—	—	—	—	6 Old healed parenchymal, right upper active?	Casts (occasional polyuria)
64	0.80	Exophthalmic goiter (recovered)	—	—	—	—	7 Ghon, left lobe	
65	0.82	Vagotonic	—	—	—	—	Hilum	
66	0.84	Neurovascular asthenia	—	—	—	—	Hilum	
			1	1	3	2	7	6

TABLE 3—Normal Student Group Arranged According to Inflammatory Index

Student	Index	University Athletics	Sensitization	History of Chemical Tuberculosis	History of Family Tuberculosis	Roentgen-Ray Diagnosis of Tuberculosis	Influenza	Scarlet Fever	Diphtheria	Albumin and Casts
6	35						—	—		
5	52	+		+	+		—	—	+	
22	58						—	+		
44	64					+	+	+		
27	65			+	+		—	—		+
10	67				+	+	+	+		+
30	67	+			+	+	+	—		
70	69						+	—		+
19	70					+	—	—		
1	71						—	—		
12	71	+					+	—	+	
92	73				+	+	+	+		
9	74						—	—		
20	74	+					—	—		
3	76	—	+				+	—		
41	77						+	—		
8	79			+	+	+	+	—		
4	81		+				—	—		
26	81						—	—		
91	83						+	+	+	+
36	85						+	+		+
24	86						—	—		
13	87				+	+	+	—		
17	90				+	+	+	—		
18	90			+		+	—	—		
29	93						—	—		
43	94						—	—	+	
2	95				+	+	—	—	+	
34	96					+	+	—		
39	100			+		+	+	—		+
45	101					+	+	—		+
47	103						—	—		
57	104					+	—	—	+	
		5	2	16			15	6	6	7
35	104						—	—		
63	105					+	+	+		+
38	105						—	—		
16	105						—	—		
21	106						—	+		
7	107	+	+				+	—		
25	108		+				—	—		
37	113				+		—	—		
60	114						+	+		
42	116				+		—	—		
28	120						—	—		
46	120						+	—		
48	120						+	+	+	
66	120						—	+		
49	121						+	—		
53	123						+	—		
56	123						+	+		
23	130	+			+	+	—	—		
61	130						+	—		
51	132						+	+	+	
33	134						+	+		
15	140					+	—	—		
58	150						+	—		
59	150			+	+	+	—	—	+	
52	150						+	—		
11	152	+					—	—		
14	155	+					+	—		+
62	170						—	—		+
40	175	+					+	—		
64	177					+	+	—		
65	182						+	—		
74	185		+				+	—		
55	185						—	—		
		5	3	7			18	9	3	2

Student 8 had a tuberculous kidney removed two years before this examination. The nonprotein nitrogen of the blood was increased to 53.

Student 1 had a moderate amount of psoriasis, student 55 some ichthyosis.

Student 59 had a duodenal ulcer (roentgenologic confirmation of occasional symptoms).

Student 64 had an active exophthalmic goiter about one year before this experiment. He is now in a stage of inactivity, with basal metabolic rate of $+8$. Some minor vasomotor disturbances remain.

Student 65 is the only one that can be classified as vagotonic. He has the lowest blood pressure, has a vagotonic epinephrine reaction, and perspires profusely on excitement.

Student 66 on examination is classified as a neurovascular asthenia patient, possibly on the basis of hyperthyroidism. The basal metabolic rate is $+8$ and he has lost some weight during the last year.

Athletics—We have limited the term to the activities of students who have made places on and have engaged in the strenuous athletic training of regular university teams (football, basketball, swimming, etc.). High school athletic activity has not been considered. It is apparent that with one exception all the athletes are in the group of relative impermeability. When we take into consideration the blister time (table 3), this difference is equalized. We can only interpret this as an indication that as a result of athletic activity—or because of the constitutional qualification involved in eligibility for athletes—these men have a capillary permeability that is lessened, but that the sympathetic tonus of the arterioles is unaltered.

Sensitization—While the cases of sensitization are not many, the results are analogous to those for athletics. In the impermeable group are four out of the five who have a history of sensitization. Classified by the inflammatory index the difference vanishes. Of these students, student 3 comes of a family in which all members have hay-fever, as has this particular student. From the age of 10 to 12 he had asthma in addition to hay-fever.

Blood Pressure (table 4)—Analyzed on the basis of capillary permeability it is strikingly evident that diminished capillary permeability is associated with increased blood pressure. On the other hand, when we use the inflammatory index there is no evident relationship between the blood pressure and the degree of reaction, unless in the very slight increase in diastolic pressure with increase in inflammatory reaction. This, if confirmed by further work, can imply but one thing. The increased blood pressure is associated with lessening capillary permeability and not with the tonus of the arteriole. We are, of course, not dealing with pathologic conditions and we cannot state that any of these men will develop hypertension.

Albumin and Casts—On the basis of permeability six of our nine students with albumin or casts in the urine belong in the permeable group, but examined on the basis of the inflammatory index this relationship is reversed and seven of the nine are in the group with low inflammatory reaction. The nine students have a permeability that

TABLE 4—*Blood Pressures Arranged According to Inflammatory Index and Permeability*

Inflammatory Index	Blood Pressures	Permeability Ratio	Blood Pressures	Men
5 2	120/80			
6 4	106/80			
6 5	116/74	0 56	118/80	
6 7	118/78	0 57	120/80, 130/80, 120/80,	
6 6	140/90		148/90	
6 9	114/84	0 59	148/84, 134/92	
7 0	116/72	0 60	118/78, 134/92	
7 1	118/80, 130/84	0 61	112/70, 134/90, 130/84	
7 3	116/68			
7 4	134/92, 128/80			
Average 12, 121/78				
7 6	130/84			
7 7	118/80			
7 9	134/92			
8 1	124/90, 120/80			
8 3	120/78	0 62	118/74	
8 5	140/90	0 63	132/90, 140/100, 116/72,	
8 6	120/80		128/80, 110/70	
8 7	134/90	0 64	130/90, 126/76	
9 0	110/70, 140/100	0 65	120/80, 120/80, 116/74,	
9 3	126/80		120/80, 110/78, 126/80	
9 4	130/86	0 66	120/78, 140/90, 116/68	
9 5	120/80	0 67	118/76, 116/68	
9 6	118/68			
10 0	116/78			
10 1	114/74			
10 3	120/90			
10 4	120/80			
Average 19, 123/78				
10 4	118/80			
10 5	118/85, 118/78, 132/90			
10 6	130/90			
10 7	148/84	0 68	118/80, 136/84, 140/90	
10 8	120/80	0 69	118/76	
11 3	136/84	0 70	116/78, 128/90, 130/86,	
11 4	122/78		118/80, 120/80, 106/80	
11 6	120/80	0 71	114/74	
12 0	110/78, 115/70, 144/90	0 72	120/80, 115/70	
12 1	138/90	0 73	114/64, 138/90, 120/78	
12 3	120/80, 128/80	0 74	128/80, 130/90, 120/85,	
13 0	126/78, 118/80		120/80, 120/80	
13 2	120/78			
13 4	118/76			
14 0	118/74			
Average 21, 124/81				
15 0	118/70, 118/76	0 75	118/70, 118/76	
15 2	112/70	0 76	122/78	
17 0	128/90	0 77	118/80, 128/90	
17 5	128/90	0 79	118/85	
17 7	(146/80)	0 80	(146/80 exophthalmic goiter)	
18 2	100/70			
18 5	120/80, 130/90	0 82	100/70	
		0 84	144/90	
Average 8, 119/80				
Average 8, 120/80				

averages 0 7 (normal 0 68) and a blister time that averages eight hours (average 7 1 hours). We regret that our series is not larger, but if we may draw any conclusions the material indicates that with evidences of kidney disturbance the capillaries have an increased permeability while the sympathetic tonus of the arterioles also is increased. We can readily

understand that such changes in the kidney would lead to an albuminuria Jaffé has discussed the underlying microscopic changes in a recent article ¹⁴

Tuberculosis—We have made a complete study of the student material to determine the relative amount of tuberculous infection—by history of familial contact, by evidences of past clinical activity and by a roentgenologic examination Arranged by permeability it will be noted that of the impermeable group fourteen have either a distinct family history a clinical history of past activity or a roentgen-ray diagnosis of parenchymal involvement (hilum tuberculosis disregarded) There are nine such cases in the permeable group This difference is accentuated in the examination on the basis of inflammatory index, in which we find sixteen in the first group and only seven in the second group Two of the students had active lesions and one was of doubtful activity roentgenologically

We are of the opinion that the increased amount of tuberculous infection that has been overcome by the students in this group has resulted in a modification of the tissue so that there is less permeability and increased sympathetic tonus of the arterioles The average blister time for the tuberculous cases was 7.4 hours (normal 7.1 hours) We shall comment on this relation in detail later

Other Infectious Diseases—When we turn to other infections, the relation of the permeability to influenza morbidity is of some interest (table 5) Exactly 50 per cent of the students report that they have had influenza at some time since 1918 The group of low permeability have had approximately half as much as those in the group with higher permeability In the case of scarlet fever (fifteen cases) the permeable group also contained more cases, while diphtheria and typhoid were about evenly divided

Arranged on the basis of inflammatory reaction the relative influenza morbidity for the groups is 44 and 56 per cent (table 2) There seems some definite relation between morbidity and permeability In view of the clinical experience that both influenza as well as scarlet fever are apt to injure the endothelial system, the logical interpretation would seem to be that these infections have left the endothelium in a more labile state than normally The other possibility that we must consider is that the impermeable person is less susceptible to the infection, for presumably the opportunity for infection has been uniform That such a possibility exists might be inferred from the influenza statistics which show the relative immunity of persons in the tuberculosis sanatoriums during the recent pandemic Patients with tuberculosis (chronic) as will be demonstrated later, are among the relatively impermeable group

14 Jaffe, R. H. Am J M Sc 169 88 (Jan) 1925

REACTION TO EPINEPHRINE

From the group we next selected men of low and high permeability (six of each) and injected 5 mm of epinephrine (1 1,000) subcutaneously. The pulse rate and blood pressure were recorded every five minutes for approximately one hour. The pulse rate times the blood pressure was calculated, preinjection figures taken as 100 per cent and changes from the normal computed in percentage of the normal figure. In chart 1 the time of maximum alteration for the two groups of students has been charted. The permeability index of the students is noted at the end of each individual curve.

TABLE 5—*Relation of Permeability Ratio to Influenza Morbidity*

Permeability Ratio	No in Group	Influenza	Scarlet Fever	Typhoid	Diphtheria
0.57	6	1			2
0.59	2	1		1	
0.60	2	1	1		
0.61	3	2		1	2
0.62	2	1		1	
0.63	5	1			
0.64	3		1		
0.65	6				
0.66	3	3	2		
0.67	2	2	2		
Total	34	12	6	3	4
0.68	3	1	1		
0.69	1			1	
0.70	6	4	1		1
0.71	1	1			
0.72	3	2	1	1	1
0.72	3	3	1		1
0.74	6	4	1		1
0.75	2	1			1
0.76	1	1	1		
0.77	2	1	1		
0.79	1	1	1		
0.80	1	1			
0.82	1	1			
0.84	1		1		
Total	66 (students)	21	9	2	5

Thirty-three have had influenza, fifteen have had scarlet fever, five have had typhoid, and nine have had diphtheria.

Of the thirty-four below the average (0.68) permeability, 35 per cent had influenza, while 65 per cent of the group above the average had influenza.

A striking difference is immediately apparent. The permeable students react with an increase of from 30 to 55 per cent, reaching a maximum no later than 30 minutes after subcutaneous injection. The impermeable students, on the other hand, have a much lower curve and the maximum in two instances is reached five minutes later. In each group one student is exceptional. In the permeable group, student 65, with a permeability ratio of 82 (potassium-calcium ratio 1.5) gives an absolutely straight line. This is our "vagotonic" student. In the impermeable group, student 12 reacts with a slight fall in the rate (permeability 61, potassium-calcium ratio 1.9).

Our interpretation is the following. In the permeable group the epinephrine is promptly absorbed and the effect on the blood pressure

and pulse rate is immediately apparent. As contrasted to the impermeable group, these students are, however, relatively vagotonic, because the local constriction of the capillaries has not caused a complete anemia and the interference with absorption entailed thereby, nor has the effect on the capillary wall itself (of the lymphatics) been sufficiently great to prevent absorption.

In the impermeable group, on the other hand, the absorption is exceedingly slow and the effect negated, not because the sympathetic system is relatively inactive but because the local sympathetic tonus is much greater. In student 12, with apparent vagotonic effect, absorption is evidently of so small a degree that the autonomic nervous system in its overcorrection to minute doses, responds with an apparent vagus effect. We have repeatedly met with such results in dogs when epinephrine is administered in oil (with a slow rate of absorption). Under such circumstances actual salivation occasionally follows epinephrine injection.¹⁵

In both these students we injected epinephrine intravenously (charts 2, 3 and 4) and plotted the systolic and diastolic pressure and pulse rate for both subcutaneous and intravenous injection. The dose was, however, not alike in the two students. The "vagotonic" student (student 65) was given 4 minims of a 1:1,000 solution, the sympathetic (student 12) 1 minim. The results are of interest from a clinical standpoint because of the frequency with which subcutaneous injections are made to determine the relative reactivity of the autonomic apparatus, and interpretations made without due consideration of the local factors involved.

Ionic Equilibrium of the Blood—We wish finally to present the results of blood analyses made on twenty-three of the men. These students were selected as representatives of different degrees of reactivity.

In table 6 we present them according to the permeability.

It will be noted that the potassium-calcium ratio of the permeable group is decidedly lower than that of the less permeable groups. There are, however, some striking exceptions of impermeable students with relatively low ratios, for example, students 11, 12 and 32.

When we now examine the same groups arranged on the basis of the inflammatory index the correlation to the blood chemistry is apparent.

From these tables it is probable that we may have relatively impermeable capillaries with a low potassium-calcium ratio, but in general increased capillary permeability parallels the lowering of the potassium-calcium ratio.

It is only when we examine the classification according to inflam-

¹⁵ Petersen, W. F. To be published.

matory index that the agreement becomes quite regular. Here there is a progressive increase in the inflammatory reactivity as the ratio becomes smaller.

We should like to emphasize these findings because of considerable confusion that exists in the interpretation of many investigations of blood calcium values.

It will be observed that there is little or no difference in the actual calcium values of the serum. The marked difference exists in the potassium values. In the impermeable group we find relatively much potassium in proportion to the calcium. This means that the condition as far as the cells are concerned is the reverse, with more calcium and less potassium in proportion. This is in agreement with what is known of the general protoplasmic effect of calcium and potassium on cellular

TABLE 6—*Relation of Permeability to Potassium-Calcium*

Student	Permeability Ratio	Calcium, Mg per 100 Cc	Potassium, Mg per 100 Cc	Potassium Calcium
2	57	10.00	19.5	1.95
4	57	9.82	25.5	2.60
6	57	10.00	25.8	2.58
9	60	8.92	22.1	2.50
10	60	10.26	21.0	2.00
11	61	10.00	18.7	1.87
12	61	10.26	19.8	1.90
17	63	9.48	25.5	2.50
18	63	9.14	24.6	2.70
21	64	9.90	21.5	2.00
25	65	9.48	26.0	2.70
Averages (11)	60	9.74	22.7	2.30
30	66	9.65	27.40	2.80
32	66	10.40	18.74	1.80
34	67	10.08	19.60	1.94
36	68	9.48	25.60	2.80
41	70	9.65	24.60	2.50
82	70	10.00	23.00	2.30
Averages (6)	68	9.87	23.1	2.34
54	74	9.35	17.35	1.90
59	75	10.00	19.03	1.90
62	77	9.90	17.10	1.72
64	80	10.26	17.30	1.60
65	82	10.08	15.05	1.50
66	84	10.08	17.61	1.76
Averages (6)	78	9.94	17.20	1.72

activity. In the group with high inflammatory index (increased permeability, short blister time) we have in the serum a larger proportion of calcium to potassium, and the cells will contain little calcium as compared to the potassium.

CHILDREN

We have had but few children in our series of normals, the group is tabulated in table 8.

In general the permeability ratio is higher than in our adult group and the blister time shortened. On the other hand, the assumption that

in infants this might be true to an even greater degree seems fallacious, for in the two cases that we have been able to observe the infant of 7 days (normal) had a ratio of only 0.63, and a three months' feeding infant a ratio of 0.74. It is to be remembered that the skin capillaries of the infant under three months differ materially in their anatomic structure from those of the normal adult.

TABLE 7—*Relation of Inflammatory Index to Potassium-Calcium Ratio*

Student	Inflammatory Index	Potassium	Blister Time in Hours	
		Calcium		
6	3.5	2.58	16	
30	6.6	2.80	10	
10	6.7	2.00	9	
12	7.1	1.90	8½	
32	7.3	1.80	9	
9	7.4	2.50	8	
41	7.7	2.50	9	
4	8.1	2.60	7	
36	8.5	2.70	8	
17	9.0	2.50	7	
18	9.0	2.70	7	
Averages (11)		7.35	2.40	9
2	9.5	1.95	6	
34	9.6	1.94	7	
82	10.0	2.30	7	
21	10.6	2.00	6	
25	10.8	2.70	6	
66	12.0	1.76	7	
Averages (6)		10.4	2.11	6.6
59	15.0	1.90	5	
11	15.20	1.87	4	
62	17.0	1.70	4½	
64	17.7	1.60	4½	
65	18.2	1.50	4½	
54	18.5	1.90	4	
Averages (6)		17.0	1.74	4½

TABLE 8—*Normal Juvenile Group*

Number	Sex*	Race	Age	Clinical Diagnosis	Blister Time in Hours	Serum Protein, per Cent	Blister Protein, per Cent	Ratio B/S	R/T
129	♀	W	7	Normal strabismus	6	8.60	6.75	0.78	13.0
128	♀	W	8	Normal strabismus	6½	8.40	6.81	0.81	12.4
126	♀	W	14	Normal, lipoma of eyelid	4½	8.28	6.80	0.82	18.2
237	♀	W	11	Elbow dislocation 2 months before examination	5	7.85	6.10	0.77	15.4
224	♂	W	12	Circumcision (24 hours previously)	5½	7.63	6.30	0.82	15.0
145	♂	W	14	Phymosis, hernia	5	7.85	5.29	0.67	13.4
146	♀	W	16	Ingrown nail	4½	7.52	5.39	0.71	15.5
179	♀	W	21	Normal (before removal of small scar)	5	7.20	5.40	0.75	15.0
B1	♀	W	7 days		6½	7.73	4.89	0.63	10.0
B1	♂	W	3 mo	Feeding case	8	5.68	4.27	0.74	9.2

* In this table, ♂ indicates male, ♀ female

SUMMARY

1 From the results obtained with the blister method we have reached the conclusion that it offers a relatively simple method of obtaining information concerning the constitutional reactivity of the individual.

2 (a) The permeability is determined by comparing the amount of protein in the blister to the serum protein (b) The degree of inflammatory reactivity (inflammatory index) is expressed by the quotient
$$\frac{\text{permeability ratio}}{\text{blister time}}$$

3 In a group of sixty-six normal students examined, the permeability ratio varied from 57 to 84, the inflammatory index from 3.5 to 18.5. Averages were 68 and 10.5, respectively.

4 In the relatively impermeable group are the university athletes and sensitized individuals, in the permeable group, the majority of students who have some evidence of kidney disturbance.

5 Examined on the basis of inflammatory reactivity, the students who have had more than the average amount of parenchymal tuberculosis are low (sympathetic), as are also the students with kidney disturbance (sympathetic tonus of arterioles, increased permeability of capillaries).

6 There is definite relation between the blood pressure and permeability.

7 There is some evidence of relationship between influenza morbidity and permeability (increased permeability following influenza and scarlet fever [?]).

8 Students in the impermeable group respond to subcutaneous epinephrine injection with less systemic vascular effect (greater local effect at site of injection).

9 There is a direct chemical basis for the differences in permeability and inflammatory response, namely, the ratio of calcium and potassium. A low inflammatory index is associated with a high blood potassium-calcium ratio, a high inflammatory index with a low potassium-calcium ratio. In the tissue cells these conditions will be reversed. The impermeable cell has in general a greater amount of calcium in proportion to the potassium, while the permeable cell has a small amount of calcium to the potassium.

10 In infants the permeability of the skin capillaries is probably not high, but in children the permeability seems definitely increased over that of the adults.

Book Reviews

THE PRINCIPLES AND PRACTICE OF ENDOCRINE MEDICINE By WILLIAM NATHANIEL BERKELEY, PH D, M D Pp 368, with index, 60 illustrations Price, \$4 50 Philadelphia Lea and Febiger, 1926

"The book is primarily meant for doctors in active practice The standpoint of the writer is that of the clinical practitioner" (preface) The book contains three introductory chapters, one on general methods, one on the autonomic nervous system, and one on basal metabolism Then follows the usual chapters on the thyroids, the parathyroids, the hypophysis, the suprarenals, the pancreas, the sex glands, the pineal body, the thymus, the intestinal mucosa and mammary glands There is one chapter on the interrelation of the glands of internal secretion, and one on forms of pluriglandular disease, and a final chapter on endocrine influence on growth, old age and obesity

The author has a clear and concise style His meaning is at no time obscure He has a good acquaintance with the great mass of scientific facts, and in most instances these are presented fairly and critically He shows less critical discrimination in the fields in which in earlier years he had personal contact with experimental work The different chapters are therefore of unequal reliability and value as guides for the general practitioner The author is at his best on the thyroids, the suprarenals and the sex glands The chapter on the pineal body is in length out of all proportion to what is known concerning the rôle of this body in health and in disease But here, as in some other cases, the author has something to sell a pineal extract which when given by mouth to "backward" children for a long time is said to improve the mentality

Some of the faulty or inadequately qualified statements of facts may be noted The author seems not acquainted with the numerous reliable researches that show no direct influence of sympathetic nerves on the tonus of skeletal muscles (pp 30, 31 and 143) He states that thyroidectomy in rabbits is without effect (p 42) This is contrary to fact "Marine's statement that the immediate cause of goiter (simple) is lack of iodine can hardly be affirmed any more than it can be claimed that the immediate cause of malaria is lack of quinine" (p 63) This is a curious lack of understanding and logic in a man who at times shows the fallacy of "the undistributed middle" in the argument of others Quinine appears to be a direct germicide, and not as iodine, a necessary element in the structure of an important hormone

Speaking of his own parathyroid preparation administered by mouth, he reports "remarkable benefits" in the majority of cases of paralysis agitans, despite the improbability of parathyroid origin of this malady, and the indication that the parathyroid hormone is ineffective by the oral route Showing good judgment in other matters, when it comes to his own parathyroid preparation he accepts support by the ordinary testimonial route "The wife of another recent patient writes, 'We are greatly encouraged and hope he will be entirely well'"

"Primary anterior lobe deficiencies of a 'functional,' or at least temporary and curable character, in boys and girls of the infantile type a long series of New York Public School children of this character have passed through my hands in the last fifteen years They receive whole pituitary (special formula prepared for me by a New York wholesaler) in suitable doses, and in the course of one or two years they grow remarkably" (p 188) We have the right to ask how much did the *control* group of similarly "temporary" infantile children grow in the same length of time?

"In the treatment of Froelich's disease the prolonged administration of whole pituitary gland preparation is the most rational procedure" (p 195), despite the evidence (Evans, Smith and others) that anterior lobe hormone is ineffective by the oral route

On page 261 he states that in diabetes he still "with satisfaction" uses his own extract of the pancreas given by mouth, despite the evidence that insulin, except in enormous quantities, is ineffective by that route

"Ligation or partial excision of the vas deferens causes a slow atrophy of the seminiferous cells" (p 271) This has been disproved by Moore and others

"A high degree of sexual ardor at the time of intercourse probably modifies favorably the growth if not the structure of the fertilized ovum" (p 295) The evidence for this is cited from *King Lear*

The author recommends pluriglandular therapies "In all cases of depressed metabolism, retarded sex development and diminished growth, thyroid and anterior pituitary and probably pineal will act synergically" (p 344)

"In frank cretinism it has seemed to me useful to supplement the action of the thyroid with whole pituitary, pineal, and the proper gonad When the patient is carefully watched pluriglandular therapy can at least do no harm" (p 345) The last statement is probably true in regard to the patient's body, but what about the patient's pocketbook and the physician's mind?

The same kind of therapy is recommended in so-called endocrine obesity "It may even be well to give thyroid, pituitary and ovarian (or testis) extract in one pill

The food supply should be slowly diminished and this medication slowly discarded until the patient loses $1\frac{1}{2}$ to 2 per cent of his body weight per month" (p 356) Why reduce the food supply if the obesity is of endocrine origin and curable by feeding endocrine mixtures? By speeding up metabolism, increasing nervous tension, and increasing the energy expenditure in muscular work, thyroid extract will by itself reduce body weight in obesity, even on a uniform intake of food

The book is written from the standpoint of the clinical practitioner for physicians in active practice But curiously enough, the author shows greater erudition, critical judgment and common sense in the presentation of the experimental data than in the presentation of the clinical data The volume is therefore a "mixed blessing" in this era of mushroom growths of monographic endocrinology

LE TERRAIN HEREDO-SYPHILITIQUE By V HUTINEL, Professeur honoraire de clinique medicale infantile et Membre de l'Academie de Medicine Pp 455 Paris Masson et Cie, 1926

The present volume is the product of the ripe experience of an eminent French pediatrician and syphilologist On page 89 he says "When I was an intern to Parrot in 1876" An internship with Parrot and fifty years of experience make an interesting introduction, and one is not disappointed The book is not a compilation and is therefore not burdened with references It is the statement of a man who knows congenital syphilis in all its manifestations from personal observation under most favorable circumstances, and over a period of many years, and who has lost none of the vigor and enthusiasm of youth in the presentation I know of no treatise on congenital syphilis in any language that presents the whole subject so exhaustively, so satisfactorily, so authoritatively, so systematically, and so fascinatingly It is the sort of a book in a short review of which it is hard to know what phase to bring into relief One cannot help, however, emphasizing as an illustration the eighteen page chapter on "l'appareil urinaire"—a convincing first hand presentation that I am sure is a revelation to most, if not indeed all, of us The same could be said of many other chapters The book can be warmly commended to both the pediatrician and the syphilologist, both because it is a most satisfactory treatise in itself and because it has that added value and interest that always attach to the personal views and presentation of a master clinician The book must be read to be appreciated

LES MALADIES DES GLANDES ENDOCRINES By PROF KNUD H KRABBE Pp 92,
25 illustrations Paris Librairie le François, 1926

This little volume is a translation into French of the chapter by Krabbe on the diseases of the endocrine glands in the Danish *Laerebog intern Medicin* (Copenhagen, 1922) There are twenty-five well selected photographic illustrations The book is a concise and conservative summary of the present status of our knowledge as to symptoms, diagnosis and therapy of the disorders of the thyroids, the parathyroids, the pituitary, the pineal, the thymus, the pancreas, the suprarenals and the gonads The last chapter is devoted to some disorders in which endocrine involvement is in doubt, such as mongolism, infantilism and osteomalacia

THE INTERNATIONAL MEDICAL ANNUAL A YEAR BOOK OF TREATMENT AND
PRACTITIONER'S INDEX FORTY-FOURTH YEAR, 1926 Cloth Price, \$6
Pp 555, with illustrations New York William Wood & Co, 1926

We have yet to see a volume of this annual that was not good It is remarkable to note as we go through this book how thoroughly and carefully recent literature is reviewed and digested And the annual really is international

Archives of Internal Medicine

VOLUME 38

DECEMBER, 1926

NUMBER 6

ANALYSIS OF HEART SOUNDS *

H B WILLIAMS, M D

AND

H F DODGE, S B, A M

NEW YORK

Certain sounds pertaining to the heart and lungs are heard in all normal persons. These normal sounds vary in quality and intensity for different individuals depending on the physical make-up of the particular organs producing them and also on the structure of bone and flesh through which the sounds are transmitted to the surface of the body. Pathologic changes can often be detected by the modification of the normal sounds or by the appearance of abnormal sounds. In this article, consideration is given to the nature of normal and abnormal heart sounds with a view to presenting preliminary information relative to their quality and frequency characteristics.

Sound is a form of vibrational energy. Sounds are created by vibrating bodies of some sort and travel through gases, liquids or solid matter in the form of compressional waves. As these waves progress through a medium they become weakened, partly because their energy is spread over a larger area as the distance from the source of sound is increased and partly by loss of energy in the particles which are set into vibration. The distance to which they will travel before the energy becomes imperceptibly small is obviously dependent on the nature of the medium through which they are being transmitted. When the path of the sound waves is abruptly changed in character, as from a liquid to a gas, much of the energy is reflected and only a small portion is passed along into the new medium. Another factor to be considered in connection with the subject at hand is that of distortion of the sounds. Distortion can be produced in certain mediums when discrimination is shown to vibrations of different frequencies, for example, if the material in the path of the waves responds more readily to low frequency than to high frequency vibrations.

In the human body the paths along which the heart and chest sounds can travel to reach the surface of the flesh are many. Much of the

* From Columbia University College of Physicians and Surgeons and the Bell Telephone Laboratories, Incorporated

energy never gets to the surface, but considering the energy that is available at the surface for auscultation, there is always a "path of least resistance" from the source of sound. The end of this path is picked out by the physician when the point of maximum intensity is found with his stethoscope. By experience it has been found that murmurs produced by lesions in the several valves of the heart are heard best in definite areas on the surface, although these areas are by no means always the nearest to the valves in question. There appear to be "characteristic areas of propagation" on the body surface which can be mapped out for particular types of lesions¹. Furthermore, the quality of the same sounds as heard in these various areas may be materially different, dependent doubtless on the nature of the particular routes traversed by them.

1 THE NORMAL HEART SOUNDS

With the electric stethoscope described in a recent article,² it is possible to reproduce the heart sounds electrically. This apparatus consists essentially of an electromagnetic detector or transmitter for picking up the sound vibrations, an amplifier for magnifying the minute electrical vibrations produced in the transmitter, and a group of electric filters for narrowing down the frequency bands of observation in order to reduce the amount of extraneous and interfering noises outside the frequency range of interest. The complex electrical waves thus produced are much more easily handled for study and analysis than the original sound waves, in view of greater facility of controlling electrical energy.

Knowledge of the frequency characteristics of heart sounds will be helpful for determining the essential requirements of any apparatus whether electrical or mechanical to be used for transmitting or reproducing them. It is of even greater importance that we know more exactly the nature of the different body sounds in order to gather fundamental data concerning organic lesions or functional disturbances with which the sounds are associated.

The first heart sound is believed to be due to vibrations set up by the heart muscle at the beginning of contraction. The second or diastolic sound is undoubtedly due to the closure of the semilunar valves.

Studies have been made of the frequency distribution of the energy of normal heart sounds as heard at the apex for ten male adults. The apparatus used for this purpose consisted of the electric stethoscope² and a special electrical frequency analyzer which made it possible to determine the relative amounts of energy in the different frequency

1 Cabot, R. C. *Physical Diagnosis*, chapter X.

2 Frederick, H. A., and Dodge, H. F. *The Stethophone, an Electrical Stethoscope*, Bell System Tech. J. **3** 531-549 (Oct.) 1924.

components of the complex electrical waves. This work has been restricted to a study of the energy above 50 cycles (vibrations per second) and chart 1 shows how the energy above this point is distributed in frequency bands of 10 cycles in width. Indications of later work point out that there is a considerable amount of energy below this point. Although data were obtained for frequencies up to 300 cycles, such a small percentage of the energy lies in 10-cycle bands above 150 cycles, that it is not possible to show the values on this chart.

The relative amount of higher frequency energy varied considerably in the ten persons. We found, for example, that in the cases in which the heart sounds were richest in high frequency components there was

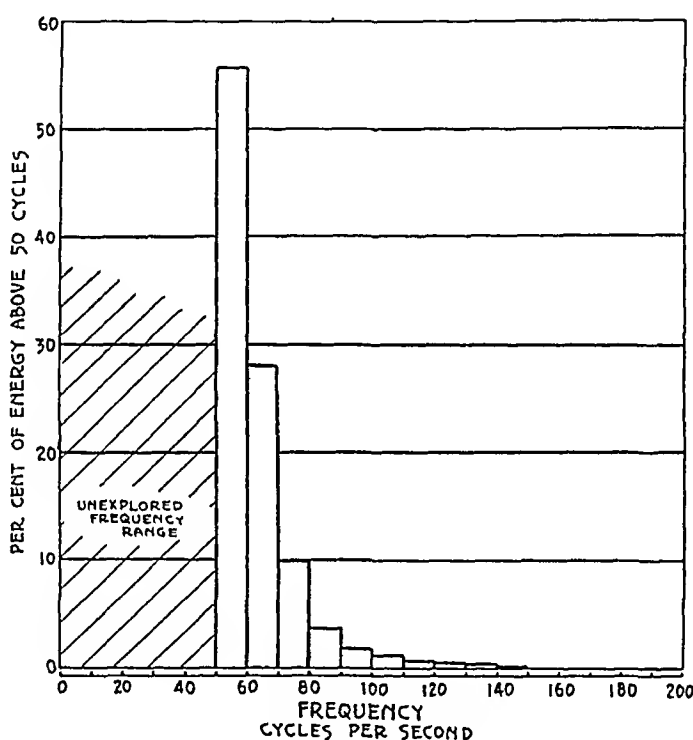


Chart 1—Energy distribution of normal heart sounds average for ten adult males

one-tenth the amount of energy in the band 90 to 100 cycles compared with the energy between 50 to 60 cycles and in the band 190 to 200 cycles, about one one thousandth of that energy. In the other extreme case in which the sounds were poorest in high frequency components the amount of energy in the band 90 to 100 cycles was one one thousandth of the energy in the 50 to 60 cycle band and between 190 to 200 cycles, approximately one one-hundred thousandth of that energy. This variation in the distribution of the vibrational energy is what determines the characteristic qualities of the heart sounds of different persons.

It is important to note that the actual distribution of energy shown in chart 1 will appear as such only when measured or recorded by instruments that are equally sensitive to all frequencies within this range. Such an instrument is the Einthoven galvanometer, which may be used to produce graphic records, examples of which will be presented in a later article. But when we observe these vibrations by ear as during auscultation, a new set of conditions exists. The normal heart sounds as heard in the physician's stethoscope are so faint that they may be considered near the threshold of audibility. For sounds near the threshold of audibility, the ear is much less sensitive to low frequency than to higher frequency sounds.³ For example, if we consider the relative sensitivity of the ear near the threshold of audibility,

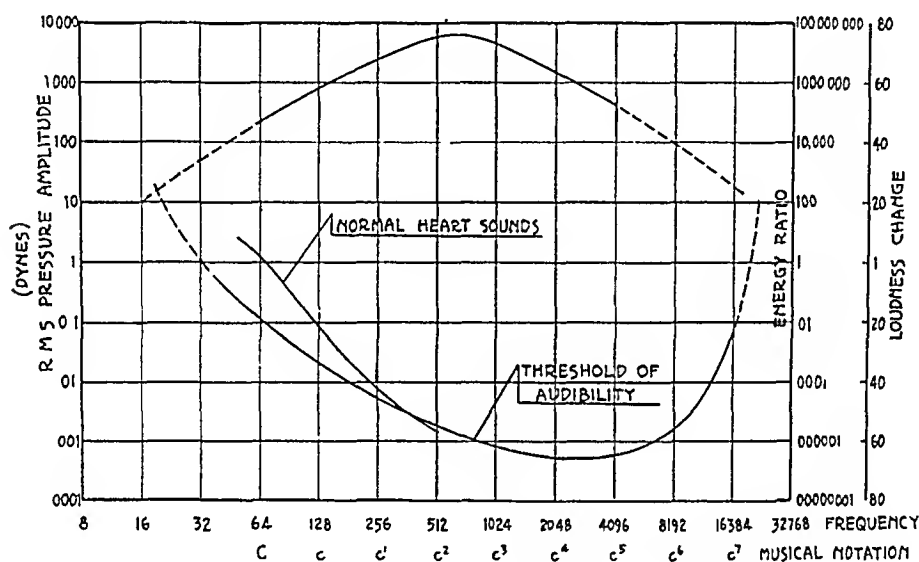


Chart 2—Normal heart sounds and the characteristics of hearing

we find that it takes over 100 times as much sound energy⁴ at 50 cycles to produce the same auditory sensation as at 150 cycles. This is a particularly important consideration for the frequency range of interest in auscultation.

Thus, if we take into account the characteristics of the ear, we get a new picture of the relative importance of the different frequency components with respect to their shares in contributing to the total loudness. Perhaps the best picture can be obtained by the curve of normal heart sound energy in conjunction with the chart of normal

3 Wegel, R. L. The Physical Characteristics of Audition, Bell System Tech J **1**, November, 1922. Fletcher, H. Physical Measurements of Audition and Their Bearing on the Theory of Hearing, J Franklin Inst **196**, September, 1923.

4 More rigorously "power" rather than "energy." If, however, all the sounds that are compared are of the same duration, comparisons will be numerically the same whether power or energy is measured.

auditory sensation area ⁵ as given by measurements of hearing (chart 2) The sensation value to the ear at any frequency for the heart sounds is measured by the difference between the average heart sound curve and that of the threshold of audibility Where the heart sound curve drops below the threshold curve, the components are not audible Due to the greater sensitivity of the ear at higher frequencies, the small amount of energy between say 100 and 300 cycles is of considerably greater importance than would appear from chart 1 For example, let us compare the two bands, 50 to 60 cycles and 140 to 150 cycles From chart 1 it is seen that the relative energy of the heart sounds in these two bands is of the order of 400 : 1 Yet, due to the greater sensitivity of the ear in the latter region, the relative sensation is considerably less than 10 : 1 From chart 2 we can see at a glance over what frequency range the audible components of average normal heart sounds extend Since the ear is customarily employed for observing the heart sounds, these factors must be considered carefully in the interpretation of any data obtained by instruments of different characteristics

The normal heart sounds of different persons have their own peculiar quality characteristics somewhat as various voices do The quality of these two kinds of sounds is a function of the frequency distribution of the energy of which they are composed Speech is produced by the vibration of the vocal cords, but the sounds so produced are subsequently modified as they pass through the vocal passages of the throat and mouth Thus, the mode of vibration of the organs of speech and the configuration of the paths through which the sounds are propelled are factors which make one voice fundamentally different from another In much the same way, the mode of production of the heart sounds and the nature of the path traversed by them gives the unique characteristics for different persons For comparative purposes, the distribution of energy in connected speech is shown in chart 3 The data for this chart are taken from a composite curve of connected speech for four male and two female voices ⁶ Chart 3 should be compared directly with chart 1 for it represents distribution of energy and does not consider the characteristics of the ear For speech, most of the energy is concentrated at relatively low frequencies, but the higher frequency elements up to 5,000 cycles are of great importance in determining the quality of the sounds produced This is substantially the case for the normal heart sounds, but the frequencies in this case are far lower and, for all practical purposes, the upper frequency limit may be considered as not higher than 400 cycles

⁵ Fletcher Footnote 3, second reference

⁶ Crandall, I. B., and MacKenzie, D. Analysis of the Energy Distribution in Speech, *Physiol. Rev.* **19** 221 (March) 1922

Aside from the consideration of quality, it may be of some interest to note the relative intensity of normal heart sounds as observed with the electric stethoscope for different persons. It was noted that for thin chested persons more energy was available at the sternum than at the apex, while for those of more solid construction the energy usually was greatest at the apex. In several cases there was no marked difference in the energy in these two areas. For purposes of study about twenty male adults were chosen, more or less at random, without any thought of having cases of extremely loud or extremely weak heart sounds. For each, the area of maximum sound intensity was selected

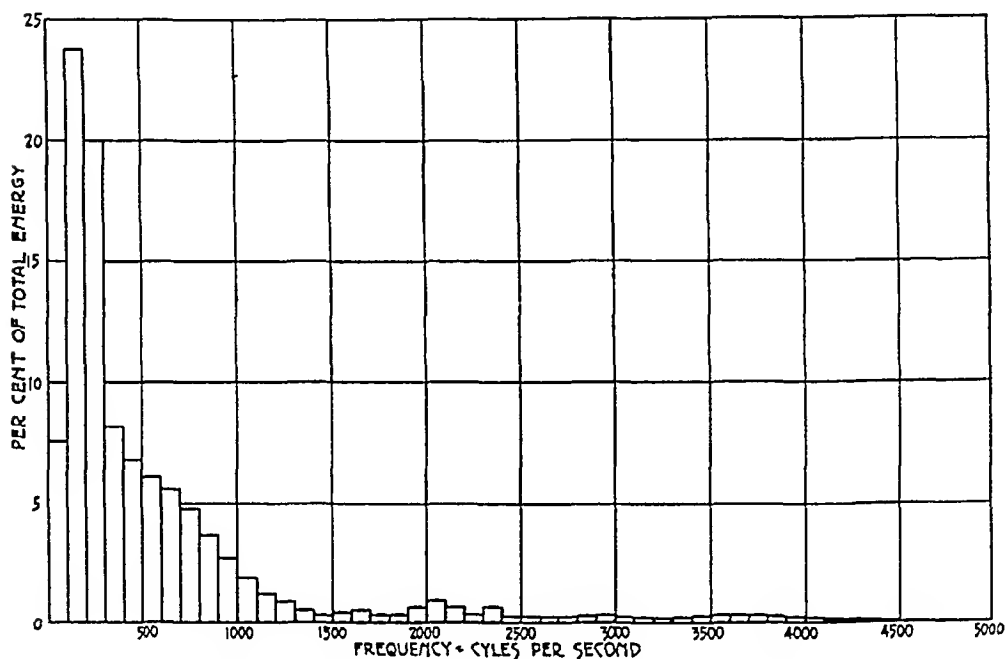


Chart 3—Distribution of energy in connected speech

and by suitable electrical measuring apparatus, the sound energy at this point was determined. In this study a ratio of over 40:1 in sound energy was observed between the loudest and the weakest normal heart sounds for the persons in the group.

2 FETAL HEART SOUNDS

So far as we have been able to determine from a limited number of cases at Sloan Hospital in New York City, the frequency composition of fetal heart sounds is similar to that of normal heart sounds. The amount of sound energy is, however, considerably smaller than for normal heart sounds. This can be visualized then by referring to chart 3 and considering the normal heart curve lowered to a position on the chart close to the threshold of audibility curve. For fetal heart sounds, therefore, the ear must operate close to the threshold of audi-

bility, and in extreme cases may be incapable of detecting the sounds. Acuity of hearing at low frequencies is obviously an essential requirement in obstetrical auscultation.

3 HEART MURMURS

The mode of origin and the character of abnormal heart sounds is well known to all physicians.

In a recent article⁷ the results of investigating the frequency bands of importance in the abnormal sounds of a large number of hospital cases of heart murmurs were given. The apparatus used in this work consisted of an electric stethoscope² provided with a group of special electric filters by means of which it was possible to determine

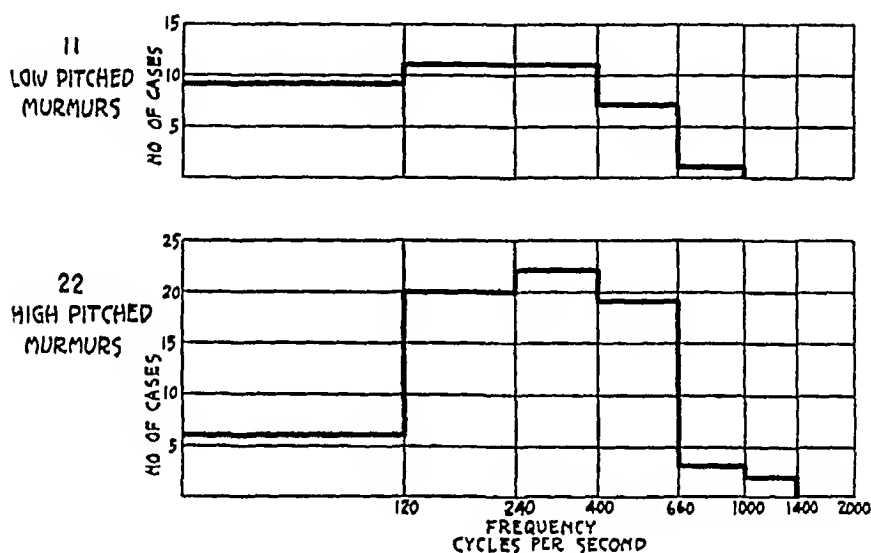


Chart 4—Composite of frequency bands for murmur sounds

the frequency band within which all the audible components of the murmur sounds fell.⁸ A study of presystolic, systolic and diastolic murmurs showed that, in general, certain fairly broad bands of frequencies could be established within which the murmur sounds of any one of these three groups could be relegated.

It is perhaps desirable to give additional data to indicate the significance of the terms "low pitched" and "high pitched" regardless of whether the sounds are associated with systole or diastole. This has been done in chart 4, data for which were obtained with electric filters

⁷ Cabot, R. C., and Dodge, H. F. Frequency Characteristics of Heart and Chest Sounds, *J. A. M. A.* **84** 1793 (June 13) 1925.

⁸ By suitable combinations of inductances and capacities, electric circuits can be produced which have the property of transmitting electric vibrations of different frequencies in a selective fashion. These circuit devices have become known as electric filters, since their action is analogous to that of a filter—Campbell, G. A. Physical Theory of Electrical Wave Filters, *Bell System Tech. J.*, November, 1922.

by the same general method as outlined in the previous article. In this figure, the composite charts are made up by adding together the frequency bands corresponding to eleven low pitched murmurs and twenty-two high pitched murmurs. The first shows that for eleven low pitched murmurs there were always components of sounds in the band 120-400 cycles per second and in nine out of eleven there were components up to 120 cycles per second. Broadly, we can think of low pitched murmurs as covering a range up to 400 cycles per second. The second chart shows that for twenty-two murmurs described as "moderately high" or "high pitched" there were always components of sound within the band 240-400 cycles per second, and nineteen times out of twenty-two, components within the band 240-660 cycles per second. From this we can consider the band 120-660 cycles as of greatest general importance for high pitched murmurs.

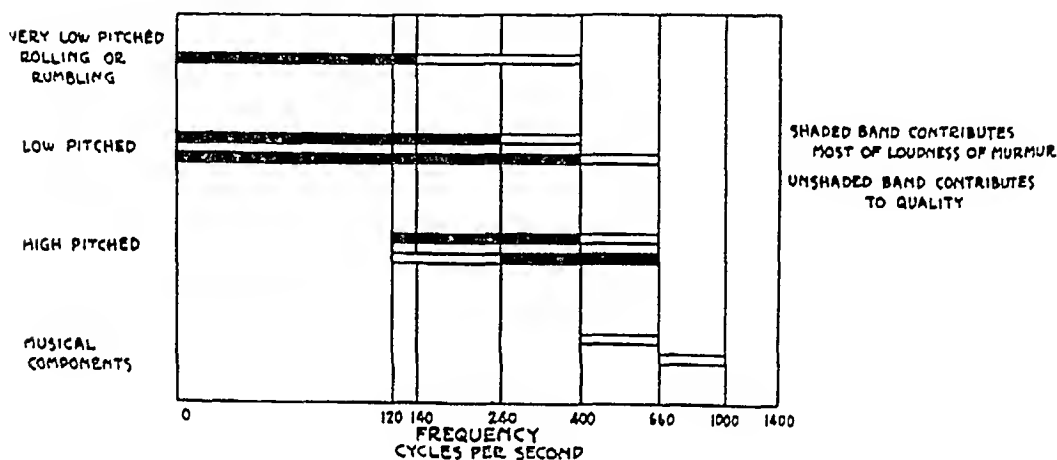


Chart 5—Representative frequency bands of certain classes of murmur sounds, shaded band contributes most of loudness of murmur, unshaded band contributes to quality

The energy of the murmur sounds is by no means distributed uniformly over the frequency band within which all the audible components are situated.⁷ If it were possible to plot a frequency distribution curve of the energy, we should undoubtedly find the shapes of the curves materially different for all murmurs. For any particular case, in a certain relatively narrow band we should find a rather large percentage of the total energy of the complex sounds and outside of this band a tapering off of energy to frequency points beyond which the amount was insufficient to give any audible sensation to the ear. It is important to note that, although the components of the sounds within such a narrow band are of major importance in fixing the "pitch" and in producing the total loudness, the remaining components outside this band are important factors in determining the quality of the sounds as a whole.

By means of electric filters and the same general method described in a previous article,⁷ we have been able to obtain a rough idea of how the total energy of murmur sounds is distributed over the frequency band which is associated with a given murmur. The method consisted in introducing into the circuit of the electric stethoscope low pass filters with successively lower cut-off frequencies and then high pass filters with successively higher cut-off frequencies and observing the resulting change in loudness without any regard for the corresponding change in quality. It was found that murmurs described as "low pitched" (or "high pitched") as a class differ greatly among themselves, depending on whether they are characterized as blowing, rasping or whistling. The results are indicated in chart 5 in which are shown the frequency bands most frequently associated with murmurs described as (1) "very low pitched, rolling or rumbling," (2) "low or moderately low pitched," (3) "high or moderately high pitched" and (4) "with musical components." The shaded portion indicates the frequency band which contributes most of the loudness while the unshaded portion indicates the band which is important only from the standpoint of quality of the complex sounds as a whole. For many individual cases the shaded portion could be narrowed down still further. Whenever the pitch could be identified with a particular musical note, it was found to correspond to some frequency within the shaded portion.

This chart indicates that most of the energy of murmur sounds is made up of frequencies below 660 cycles per second. Occasionally, components of sound are present above this frequency, particularly musical components, but these do not usually have any particular relation to the more energetic constituents of the murmur.

THE MECHANISM OF PAIN IN GASTRIC AND IN DUODENAL ULCER

II THE PRODUCTION OF PAIN BY MEANS OF CHEMICAL IRRITANTS

WALTER LINCOLN PALMER, M D

CHICAGO

Experimental data are presented here regarding the rôle of chemical irritants in the production of ulcer distress. Gastric ulcer and duodenal are considered together because the mechanism of pain in each has been found to be essentially the same.

LITERATURE

The older clinicians, like Talma¹ and Riegel,² apparently felt that the pain of uncomplicated ulcer was in some way related to the acidity of the gastric content, but they recognized gastric peristalsis and coarse food as possible additional factors. These men debated, not the mechanism of ulcer pain, but rather the occurrence of pain from hyperacidity without a definite organic lesion. Lowenthal,³ Schmidt,⁴ Boring⁵ and Hurst⁶ introduced various amounts of hydrochloric acid into the stomach in strengths varying from 0.5 to 2 per cent. They failed to produce pain either in normal persons or in patients with ulcer. Hardt⁷ reported that distress caused by ulcer might even be relieved by 0.3 per cent hydrochloric acid. Reynolds and McClure⁸ poured acid directly onto a duodenal ulcer by means of a Rehfuß tube without producing pain. These negative results were widely accepted as conclusive evidence against the acid origin of gastric distress. Bonminger⁹ had reported in 1909, however, that the distress of gastric ulcer could be brought on regularly by the introduction into the empty stomach of from

1 Talma. Zur Behandlung von Magenkrankheiten, *Ztschr f klin Med* 8 407-417, 1884

2 Riegel. Nothnagel's System of Medicine, Diseases of Stomach, London W B Saunders Company, 1915, p 579

3 Lowenthal. *Berl klin Wchnschr* 29 1188, 1892

4 Schmidt, J E. *Mitt a d Grenzgeb d Med u Chir* 19 278, 1909

5 Boring. *Am J Psychol* 26 48 (Jan) 1915

6 Hurst, A F. *The Sensibility of the Digestive Tract*, London

7 Hardt, L L J. Pain in Active Pathologic Processes in Stomach or Duodenum, *J A M A* 70 837 (March 23) 1918

8 Reynolds, L, and McClure, C W. Motor Phenomena Occurring in Normal Stomachs, in Presence of Peptic Ulcer and Its Pain, as Observed Fluoroscopically, *Arch Int Med* 29 1-11 (Jan) 1922

9 Bonminger. *Berl klin Wchnschr* 45 396, 1909

100 to 200 cc of decinormal hydrochloric acid. This work was overlooked, apparently, or at least it was overshadowed by the numerous negative results. Sippy¹⁰ found clinically that the pain of ulcer was practically always associated with a rather high degree of free acid in the gastric content obtained at the time of distress. He admitted that an equally high free acidity might be present at other times without distress. This he explained on the basis of decreased sensitiveness of the exposed nerve endings.

THE EFFECT OF ACID INJECTIONS IN NORMAL STOMACHS

The fact that gastric distress is not experienced every day by persons with perfectly normal stomachs, the contents of which may have a relatively high degree of free acid, is in itself conclusive evidence that normal gastric acidities do not produce distress in the normal stomachs of normal persons. Observations with stronger solutions have been made by other observers, as has been noted, but more information is necessary if one contemplates a comparative study of the effect of acid solutions in different types of stomachs. Normally, the gastric free acidity rarely exceeds 0.5 per cent. Hence, a study was made of the effect of injecting acid of this strength into thirty normal empty stomachs by means of a Rehfsuss tube. The unit of concentration was 0.5 per cent hydrochloric acid, the unit of amount was 200 cc, the unit of time, thirty minutes, the usual number of injections in each experiment, two, the total amount of acid given, 400 cc, the total length of the experiment, one hour. The results are shown in table 1. In twenty-nine of these patients, there was no sensation comparable to ulcer distress, in one, a slight burning developed, in seven, nausea was present, and in four, vomiting occurred. In a later series, it was thought that the percentage experiencing a slight burning was rather higher than in this first series. In one case in which acid was injected into the lower end of the esophagus, an intense burning was noticed. Nausea and vomiting seemed to occur only when the acid entered the duodenum. The injection of acid directly into the duodenum resulted in nausea, retching or vomiting almost immediately in a high percentage of cases. Large amounts of 0.5 per cent acid, 600 cc or more, were frequently retained in the normal stomach for an hour or longer without distress other than a sensation of a slight burning or warmth in the epigastrium. The pylorus frequently failed to prevent the acid solution from reaching the duodenum in such quantities and concentrations as to cause vomiting. Strong alkalis, such as tenth normal sodium hydroxide, had a similar effect either when introduced into the duodenum directly or when the

¹⁰ Sippy, B. W. *Oxford Medicine*, New York, Oxford Univ. Press, vol. 3, p. 132.

pylorus failed to retain them in the stomach until neutralization occurred. The pylorus seems to open more readily to alkalis than to acids.

THE EFFECT OF ACID INJECTIONS IN PATIENTS WITH ULCER

In considering the results of similar injections made into the stomachs of patients with ulcer, it is necessary to bear in mind that there are times, apparently, in which the pain producing mechanism of the ulcer is insensitive to the normal stimulus. It may remain so for days, weeks or months. During such periods it might be insensitive to an artificial stimulus as well. This differentiation has been found to be of great importance, as is shown in table 2, which comprises a list of twenty-five patients in whom the acid injections produced no distress other than that seen in normal persons. The old ulcer distress was not reproduced at any time. Thirty-five of the thirty-nine tests were made at a time when the pain producing mechanism was not sensitive to the normal irritant, as was evidenced by the fact that the patient was in a distress-free period. A distress-free period was considered as one in which spontaneous pain was absent for the twenty-four hours preceding the test. Four of the tests were made during a distress period and yet no pain resulted. The length of the experiment was prolonged frequently in the study of this group, 200 cc. of the acid solution being given every thirty minutes for three injections. The stomach was emptied in each case before the first injection and again at the end of the test.

The third table shows the results obtained in eighty-four patients in whom injection of the acid initiated typical ulcer distress 324 times. There were only ten failures in this group in distress periods, as opposed to seventy in distress-free periods. The majority of the distress-free periods were induced by treatment. In those cases in which distress appeared after the first or second injection, the experiment was discontinued without further injections. At times, pain was produced by the injection of small amounts of acid directly into the duodenum at the site of an active sensitive ulcer. The distress produced was in nearly every instance the patient's usual ulcer distress, typical in type and in location, and recognized by him as such. It varied in intensity in the same person and in different persons. In some it was only a mild distress, occasionally barely noticeable. These were usually persons with little spontaneous pain. In others, the distress produced appeared objectively to be as excruciating as that seen in any condition, sufficient to cause the patient to groan, perspire, writhe and even to roll on the floor in extreme agony. This distress would be relieved immediately or within thirty or forty minutes by emptying the stomach or by neutralizing the acid with alkali or cold egg-nog, or by a combination of these procedures.

The evidence that this distress is real ulcer distress is as follows

1 The patient recognizes it as his typical distress, identical in type and in location with that which he usually experiences

2 Such distress is not produced by similar injections into normal stomachs

3 The sensitiveness of the pain producing mechanism decreases as the ulcer heals This is followed most easily in gastric ulcers with penetrating defects

4 Ulcers found healed at laparotomy have been found to be acid insensitive before operation in every case tested so far (The reverse is not true Open ulcers may be insensitive to the acid as well as to the normal irritant)

TABLE 1—*Effect of Injection of Five-Tenths Per Cent Hydrochloric Acid Solution in Control Group*

Number studied	30
Pain produced	0
Slight burning	1
Nausea	7
Vomiting	1

TABLE 2—*Patients with Ulcer in Whom Typical Distress Was Not Produced by the Injection of Five-Tenths Per Cent Hydrochloric Acid Solution*

Location of Lesion	Number of Patients	Failures	
		In Distress Period	In Distress Free Period
Duodenal	16	4	17
Gastric	8	0	15
Multiple gastric and duodenal	0		
Recurrences after gastro enterostomy	1	0	3
Total	25	4	35

The seventy failures during a distress-free period are not difficult to understand Many of them were in persons who had become pain-free on ordinary ward diet, but the majority were in persons who had become pain-free as a result of antacid ulcer therapy They were acid sensitive prior to the beginning of treatment and gradually became acid insensitive, as was indicated by their ability to tolerate three injections of 200 cc of 0.5 per cent hydrochloric acid solution, 600 cc in all, for the entire period of one and a half hours without any of their original ulcer distress These seventy failures, as well as the thirty-five in table 2, making 105 in all, seemed to be due to a decrease in the sensitiveness of the pain producing mechanism

The ten failures during a distress period (that is, at a time when spontaneous distress had been present within the preceding twenty-four hours) are perhaps a little more difficult to understand There were

four such failures in table 2, making a total of fourteen. It is to be noted that eleven of these fourteen occurred in duodenal ulcers. Some of these failures are thought to have been due to persistent closure of the pylorus, as is evidenced by the recovery at the end of the test period of the entire amount of fluid injected. In such cases, the acid did not come into contact with the ulcer, but in others the stomach emptied fairly rapidly, and this explanation does not suffice. It is possible that such failures as well as the three in the gastric ulcer group may have been due to an unusually long latent period. The distress produced by the acid appeared in many instances during the first injection, in others, it appeared several minutes later, and in others it did not appear until after the second or third injection. Perhaps in a few cases in which it did not appear at all, the latent period exceeded the hour or hour and a half which constituted the length of the experiment.

It must be admitted that the concentration of the acid used in these experiments is much higher than that usually encountered in clinical gastric analyses. Can these results be duplicated or confirmed by the use of definitely physiologic concentrations? The following protocol is one of several which show conclusively that it can be.

EXPERIMENT 359—Patient J. A. Active duodenal ulcer

11 30	Lunch		
12 45	Pain appeared		
2 00	Pain worse than it had been for weeks		
2 45	Pain somewhat less	Stomach emptied of 50 cc of gruel	Free acidity, 58, total, 108
2 52	Pain entirely gone		
3 00	100 cc of hydrochloric acid solution	Free acidity, 52, total, 55	
3 08	Pain reappeared		
3 22	Pain disappeared		
3 40	Stomach emptied of 50 cc of gruel	Free acidity, 29	total, 41
3 50	Pain reappeared		
4 00	Pain very severe		
4 03	Stomach emptied of 75 cc of liquid	Free acidity, 31, total, 41	Pain relieved immediately
4 18	100 cc of hydrochloric acid solution	Free acidity, 40, total, 43	
4 28	Mild distress appeared		
4 35	Pain disappeared	Stomach emptied of 45 cc of liquid	Free acidity, 33, total, 44
4 50	100 cc of hydrochloric acid solution	Free acidity, 30, total, 32	
4 53	Mild distress appeared		
5 20	Pain continued quite severe	Stomach emptied of 25 cc of clear juice	Free acidity, 35, total, 43
5 28	Pain entirely gone		
5 30	100 cc of hydrochloric acid solution	Free acidity, 19, total, 21	
5 45	No distress	Stomach emptied of 70 cc of liquid	Free acidity, 43, total, 51
5 54	100 cc of hydrochloric acid solution	Free acidity, 52, total, 55	
6 05	Pain appeared		
6 07	Pain quite severe, patient groaning	Stomach emptied of 65 cc of clear liquid	Free acidity, 54, total, 61
6 21	Pain gone		

Here the typical pain was relieved by emptying the stomach of 50 cc of gruel with a free acidity of 58, it reappeared after the injection of 100 cc of acid with a free acidity of 52, and it disappeared when the free acidity of the content fell to 29. Further injections of solutions with free acidities of 51, 40 and 30, all produced distress which was relieved by emptying the stomach. Distress was not produced by a similar amount with a free acidity of 19. It seems probable that it would have resulted within a few minutes if the period of observation had been extended, for the free acidity was rapidly rising, due apparently to active gastric secretion. It did reappear following the injection of a solution whose free acidity was slightly higher, but still lower than that found in the original gastric content. It is apparent, therefore, that ulcer pain which has been relieved by emptying the stomach can be made to reappear by the injection of adequate amounts of hydrochloric acid in strengths no greater than that present at the time of distress, i. e., in perfectly physiologic concentrations.

The previous experiments definitely establish the fact that typical ulcer distress can be initiated by the introduction of a chemical irritant into the stomach at a time when the pain producing mechanism is known to be sensitive to the normal irritant. The chemical irritant used was hydrochloric acid varying in concentration from 0.5 per cent to the perfectly normal and physiologic strengths of 0.2 and 0.1 per cent. Typical ulcer distress was produced and relieved at will by the injection and withdrawal of the acid solutions. If the normal irritant to the pain-producing mechanism resides in the gastric content, withdrawal and reinjection of this material should have an effect similar to that of the acid solutions. The following protocol illustrates one of the several experiments which show that it does have such an effect.

EXPERIMENT 370—Patient A. G. Active duodenal ulcer

7 00	Ward breakfast
9 50	Typical pain appeared
10 10	Stomach emptied of 140 cc of thin gruel. Free acidity, 37, total, 77
10 15	Pain entirely gone
10 22	120 cc of gruel emptied at 10 10 reintroduced
10 40	Pain returned
10 54	250 cc of cold egg-nog
11 00	Pain entirely gone

Typical distress was present in this experiment, with a normal free acidity of 37, this distress was relieved in five minutes by emptying the stomach, it returned eight minutes after the gruel had been reintroduced, and it was relieved by 250 cc of cold egg-nog. The gastric content, therefore, does contain a normal irritant to the pain producing mechanism.

If hydrochloric acid is a normal irritant, pain should result at times in sufficiently sensitive mechanisms from the presence in the

stomach of pure gastric juice, especially if the concentration of acid be high. This might occur spontaneously or as a result of the stimulating effect of histamine hydrochloride given hypodermically. Such observations were made and repeatedly confirmed in the manner typified in the following protocol •

EXPERIMENT 393—Patient C F Active duodenal ulcer

- 6 33 200 cc of 0.5 per cent hydrochloric acid Pain appeared during injection
Stomach emptied immediately of 210 cc of clear liquid Free acidity, 150, total, 154 Pain relieved immediately
- 6 38 200 cc of 0.25 per cent hydrochloric acid solution
- 6 40 Pain appeared
- 6 45 Stomach emptied of 200 cc of clear liquid Free acidity, 81, total, 84
- 6 47 200 cc of hydrochloric acid solution Free acidity, 50, total, 51 Pain appeared during injection, very mild
- 6 51 Stomach emptied of 150 cc of clear liquid Free acidity, 58, total, 62
The pain was relieved immediately
- 6 54 200 cc of hydrochloric acid solution Free acidity, 39, total, 40
- 7 00 Pain appeared, very mild
- 7 03 Stomach emptied of 110 cc of clear liquid Free acidity, 48, total, 52
- 7 04 Pain gone
- 7 07 200 cc of hydrochloric acid solution Free acidity, 24, total, 26
- 7 18 200 cc of hydrochloric acid solution Free acidity, 24, total, 26 Heaviness but no other distress
- 7 23 Very faint distress appeared, almost difficult to recognize
- 7 26 Stomach emptied of 170 cc of liquid Free acidity, 39, total, 42 Distress relieved immediately
- 8 15 Pain appeared
- 8 23 Stomach emptied of 40 cc of gastric juice Free acidity, 82, total, 91
- 8 33 Pain entirely gone
- 8 50 Stomach emptied of 10 cc of gastric juice Free acidity, 89, total, 101
- 8 58 125 mg of histamine subcutaneously
- 9 07 Pain appeared
- 9 10 Stomach emptied of 20 cc of cloudy gastric juice Free acidity, 86, total, 93
- 9 13 Pain entirely gone
- 9 26 Pain appeared, worse than last time
- 9 30 Stomach emptied of 55 cc of cloudy juice Free acidity, 100, total, 107
- 9 40 Pain continued Stomach emptied of 55 cc of cloudy juice Free acidity, 108, total, 116
- 9 45 Pain entirely gone

The patient was seated in a chair during this experiment, and his mind was centered largely on the smoked drum which was revolving before him registering his hunger contractions from time to time. He had no knowledge of the solutions that were being used or of their purpose. His only instructions were to sit still, to avoid coughing if possible, to notify the observer whenever the water manometer failed to work properly, and to indicate the appearance and disappearance of distress. No suggestion was given him as to the time at which he might expect distress or as to what might relieve it. The results obtained were so constant with him and with other patients as well that mental suggestion cannot be considered to have been a factor.

The first half of this experiment again illustrates the production of pain by the injection of physiologic strengths of the acid, and the manner in which the severity of the pain decreases as the acid concentration of the solution decreases until with a free acid of 24 no distress was produced. When the gastric secretion had raised the free acidity to 39, a very faint distress appeared. Here there is a suggestion of a quantitative relationship between the concentration of the acid and the severity of the pain.

In the second part of the experiment, pain appeared spontaneously, and it was relieved by emptying the stomach of 40 cc of gastric juice having a free acidity of 82. At 9 07, following the histamine injection, pain appeared and was relieved again by emptying the stomach. At 9 26 pain reappeared, more severe than before, but this time it was not relieved by emptying the stomach at 9 30. The reason is obvious, for ten minutes later when the stomach was emptied again another 55 cc of gastric juice was obtained with a free acidity of 108. Relief was complete five minutes later. Here ulcer distress is clearly shown to have been present when the stomach contained only its own gastric juice, and to have been relieved by the removal of this juice.

Can ulcer distress be initiated by the introduction into the stomach of the gastric juice of another person, and, if so, is there any relationship between its free acidity and its pain-producing power? The following protocol answers the question in an illustrative fashion.

EXPERIMENT 378—Patient A G Active duodenal ulcer

- 4 59 200 cc of 0.5 per cent hydrochloric acid solution
- 5 07 Pain appeared
- 5 20 Stomach emptied of 240 cc of clear liquid Free acidity, 101, total, 109
- 5 23 Pain entirely gone
- 5 27 100 cc of gastric juice injected Free acidity, 95, total, 105 Gastric juice obtained in another patient by histamine stimulation
- 5 40 Pain appeared
- 5 48 Stomach emptied of 110 cc of clear juice Free acidity, 59, total, 70
- 5 50 Pain entirely gone
- 6 02 200 cc of gastric juice the acidity of which had been lowered from 100 to 0 by calcined magnesia and sodium bicarbonate
- 7 02 No pain Stomach emptied of 80 cc of clear light yellow liquid Free acidity, 32, total, 43
- 7 09 200 cc of 0.25 per cent hydrochloric acid solution
- 7 11 Pain appeared
- 7 17 Stomach emptied of 225 cc of clear liquid Free acidity, 65, total, 72
- 7 22 Pain entirely gone

Here pain was produced by the pure acid solution and relieved by its withdrawal, it was produced again by highly acid gastric juice and relieved by its withdrawal; but it did not result from the injection of gastric juice whose free acidity had been neutralized by alkali.

Since pain resulted alike, therefore, from the introduction into the stomach of acid gastric content, of physiologic concentrations of hydro-

chloric acid, and of highly acid gastric juice, and was relieved by the withdrawal of this solution, and since pain did not result from the same gastric juice when its free acid had been neutralized, it must be concluded that the acid was the irritant common to the three pain-producing solutions, and that it was responsible for the initiation of the pain in each instance

TABLE 3—*Patients with Ulcer in Whom Typical Distress Was Produced by Injection of Five-Tenths Per Cent Hydrochloric Acid Solution*

Location of the Lesion	Number of Patients	Successes	Failures	
			In Distress Period	In Distress Free Period
Duodenal	49	185	7	51
Gastric	29	119	3	12
Multiple gastric and duodenal	2	13	0	3
Recurrence after gastro enterostomy*	4	7	0	4
Total	84	324	10	70

* Jejunal ulcer proved at operation in one case

THE EFFECT OF OTHER CHEMICAL IRRITANTS ON THE PAIN-PRODUCING MECHANISM

If the action of the acid is purely that of a chemical irritant it ought to be possible to obtain similar results in sufficiently sensitive mechanisms by means of other chemical irritants. This has been found to be the case. Solutions of sulphuric acid, acetic acid and sodium hydroxide were tried and distress produced, although not with the same constancy as with hydrochloric acid. The solutions of sulphuric acid and of sodium hydroxide gave rather severe distress in some instances, but acetic acid with its very low free acidity and poor ionization gave only mild distress, as is noted in the following protocols

EXPERIMENT 373—Patient G N Active duodenal ulcer

4 00 200 cc of 0.25 per cent hydrochloric acid solution
 4 08 Pain appeared
 4 18 Pain severe, went through to the back Stomach emptied of 75 cc of clear liquid Free acidity, 22, total, 32
 4 25 Pain entirely gone
 5 30 200 cc of sulphuric acid solution Free acidity, 99, total, 101
 5 32 Pain appeared
 5 37 Stomach emptied of 160 cc of clear liquid Free acidity, 79, total, 86 Pain relieved immediately
 5 43 200 cc acetic acid solution, approximately 3 per cent Pain appeared immediately, burning in type, more generalized than the previous distress and associated with nausea
 5 52-6 00 Stomach emptied of 225 cc clear liquid Free acidity, 10, total 485
 6 07 Distress entirely gone

EXPERIMENT 369—Patient J A Active duodenal ulcer

4 29 55 cc of gastric juice reinjected Free acidity, 96, total, 106
 4 33 Pain appeared

4	39	Pain quite severe	Stomach emptied of 40 cc of clear liquid	Free acidity 71, total, 85
4	53	Pain entirely gone		
4	58	55 cc of gastric juice emptied	Acidity reduced by sodium hydroxide to free acidity, 6, total, 16	
5	13	Mild distress reappeared		
5	16	Stomach emptied of 50 cc of clear liquids	Free acidity, 33, total, 48	
5	22	Pain entirely gone		
5	26	100 cc of tenth normal sodium hydroxide injected	Distress appeared immediately, "pretty bad," and accompanied by nausea	
5	35	Nausea gone, pain continued		
5	39	Pain entirely gone	Stomach emptied of 35 cc of clear liquid, alkaline to phenolphthalein	

TABLE 4—*Pain with Other Chemical Irritants*

Location of Lesion		Number of Patients	Successes	Failures
0.4 per cent Sulphuric Acid Solution				
Gastric		2	2	0
Duodenal		2	2	0
Total		4	4	0
3 per cent Acetic Acid Solution				
Gastric		3	3	1
Duodenal		2	2	0
Total		5	5	1
Tenth Normal Sodium Hydroxide				
Gastric		4	5	5
Duodenal		4	2	2
Gastric and duodenal		2	4	4
Total		10	11	11

TABLE 5—*Types of Extragastric Abdominal Distress Tested with Acid Injections*

Diagnosis	Number of Cases	Pain Produced by Acid	Pain Altered by Acid
Tabetic crisis	1		0
Acute cholecystitis	4		0
Chronic cholecystitis and cholelithiasis	1	0	
Cholangitis with jaundice	1		0
Subacute appendicitis	1		0
Acute enteritis	1	0	
Subacute suppurative colitis	1	0	
Functional bowel distress	2	0	
Tuberculous peritonitis	2		0
Tuberculous peritonitis and cirrhosis of the liver	1		0

The first protocol again illustrates the production of pain by hydrochloric acid, and later its production by solutions of sulphuric and acetic acid. In the second, pain is produced in four minutes by the injection of gastric juice with a free acidity of 96, but when the acidity is lowered to 6, the latent period is prolonged to fifteen minutes, and then the free acidity is found to have risen to thirty-three. The injection of tenth normal sodium hydroxide brought on distress immediately. It lasted thirteen minutes and then disappeared spontaneously as the gastric secretion reduced the alkalinity. A summary of the results obtained with these different solutions is shown in table 4.

THE EFFECT OF THE ACID INJECTIONS IN OTHER
ABDOMINAL CONDITIONS

The mechanism of pain in carcinoma of the stomach is to be discussed in detail later. The introduction of 0.5 per cent hydrochloric acid in the manner described, however, did produce pain nineteen times in eight different patients. In five other patients, the acid produced only a slight burning or no distress at all.

It was shown in the first table that in persons suffering from diseases not essentially related to the gastro-intestinal tract, the acid injections produced no distress other than slight burning, nausea or vomiting. No especial significance is to be attached to these reactions, therefore. The question arises, however, as to whether or not there are conditions other than those of ulcer and carcinoma in which the patient's typical distress may be produced and relieved at will by means of the acid injections. Was there any evidence of gastric hyperesthesia in abdominal conditions not producing ulcerative lesions of the stomach or duodenum? The conditions studied are listed in table 5. In those in which pain was already present, it was not altered by the injection of the acid, in those in which it was absent, it was not initiated by the injection.

There were five cases in which a diagnosis of peptic ulcer was made, but in which roentgen-ray examination failed to reveal any confirmatory evidence. In these five cases, the typical distress was reproduced nine times. Roentgen-ray examination is not expected to show more than about 90 per cent of ulcers, and hence it is entirely fair to consider these five, comprising only 5.6 per cent of the ulcer cases in which pain was produced by the acid as cases of ulcer without roentgen-ray evidence. The patient's typical distress was produced twice in a case that was considered as a possible syphilis of the stomach, but in which no definite diagnosis was made. Of the six cases in this group, then, in which the acid injections did initiate the patient's typical distress, five may be classed quite fairly as cases of peptic ulcer without roentgen-ray examinations, the sixth patient left the hospital symptom-free without a more definite diagnosis than that of syphilis having been made and with only antisyphilitic treatment having been given.

In this entire series of experiments, there is no definite evidence of gastric hyperesthesia in the absence of an organic lesion of the mucous membrane. The only distress produced by the action of 0.5 per cent hydrochloric acid on an intact gastric mucosa was a slight burning. The rapid entrance of acid into the intestine at times produced nausea, retching and vomiting, occasionally, severe cramps and diarrhea.

COMMENT

In the foregoing pages, it has been shown that the introduction of 0.5 per cent hydrochloric acid solution into normal stomachs may produce either no sensation or one of epigastric burning or warmth. The rapid entrance of acid into the duodenum may produce nausea and vomiting. Flushing of the face and headache have been seen occasionally as the result, apparently, of either chemical or mechanical irritation of the duodenum. In patients afflicted with a gastric or duodenal ulcer which was known to be sensitive to the normal irritant, the injection of 0.5 per cent hydrochloric acid solution produced distress which the patient identified as his typical distress in more than 95 per cent of the tests. This distress was produced and relieved at will by perfectly physiologic concentrations of acid. Spontaneous ulcer distress was relieved similarly by emptying the stomach, and initiated again by reintroduction of the aspirated content. Hence, the gastric content contained an irritant to the pain-producing mechanism. Hydrochloric acid was the only irritant common to the two solutions. Pure gastric juice with a high free acid was an adequate stimulus to the pain-producing mechanism, but gastric juice whose free acidity has been neutralized by alkali was not. Hydrochloric acid, therefore, is the irritant common to those different solutions which constituted an adequate stimulus to the pain-producing mechanism. At times, the relationship between the concentration of the acid and the severity of the pain seemed to be an almost quantitative one.

In sufficiently sensitive mechanisms, distress may be produced by the injection of solutions of other chemical irritants, such as sulphuric acid, acetic acid and sodium hydroxide. In all cases, the distress produced is relieved by the removal of the chemical irritant from the stomach or by its neutralization or by both. This evidence further supports the view that the action of hydrochloric acid is that of a chemical irritant.

The latent period is a matter of considerable interest. In duodenal ulcers, it might be explained at times by failure of the pylorus to open. In gastric ulcers, this explanation does not suffice. In very sensitive mechanisms, injection of the acid may produce distress immediately, in less sensitive ones, several minutes may elapse, even an hour or more, and in still less sensitive ones, the latent period may be longer, apparently, than the duration of the test. Similarly, the duration of the pain after removal or neutralization of the irritant may vary. At times it disappears immediately, more frequently it gradually diminishes and completely disappears within thirty minutes, rarely forty minutes. In very sensitive mechanisms, the distress may begin as a severe pain, more frequently it comes on gradually, and then increases in severity more or

less rapidly. As the sensitiveness of the ulcer decreases, the latent period gradually lengthens, the severity of the distress diminishes, the pain threshold rises, and finally it becomes completely insensitive to 600 cc. of 0.5 per cent hydrochloric acid for one and a half hours.

The variable factors on which the production of pain with solutions of hydrochloric acid depends may be enumerated as follows: (1) the sensitiveness of the pain-producing mechanism, (2) the concentration of the acid, (3) the amount of acid used, (4) time, (5) the rate of emptying of the stomach and (6) the rate and amount of the duodenal regurgitation of bile and pancreatic juice.

The severity and duration of the pain depend on these factors also. No definite relationship was found between the severity of the pain and the size or depth of the ulcer. In one case in which excruciating pain was seen the only lesions found at laparotomy were multiple superficial gastric ulcers, none of which penetrated to the serosa.

The only other condition in which acid injections have been found to give results definitely simulating those obtained with an active peptic ulcer is that of carcinoma of the stomach, which is, of course, the only other common cause of gastric ulceration. No evidence has been obtained that hyperacidity regularly produces distress in the absence of a definite organic lesion.

It cannot be assumed from the foregoing work that hydrochloric acid constitutes the only normal stimulus to the pain-producing mechanism of peptic ulcer. It is conceivable that rarely in complicated ulcers the mechanical irritation of coarse food might be sufficient to produce distress. No evidence for this has been found during the course of the present work. Spontaneous ulcer pain without free acid in the gastric content removed at the time of distress has been seen only once and that in a patient with an extremely sensitive pain-producing mechanism. Occasionally, ulcer pain has been seen as the result of external mechanical traumatism to the pain-producing mechanism. The rôle of muscle tension in the distress initiated by hydrochloric acid, and its rôle as a direct mechanical irritant of the pain-producing mechanism, will be considered in the next section.

CONCLUSIONS

1 Typical ulcer distress can be initiated in ulcer patients under suitable conditions by (*a*) the reinjection of the gæle obtained at the time of distress, (*b*) solutions of hydrochloric acid of similar concentrations (and therefore entirely physiologic) or by stronger solutions, (*c*) solutions of sulphuric and acetic acids and of sodium hydroxide.

2 Such distress is not produced in normal stomachs by similar injections.

3 Distress so produced is relieved by neutralization of the chemical irritant, or by partial removal of the irritant and neutralization of the remainder

4 Hydrochloric acid is the irritant normally present in the gastric content which constitutes an adequate stimulus to the pain-producing mechanism of a sensitive peptic ulcer

5 The distress of gastric carcinoma can be similarly induced at times

6 The distress typical of the other abdominal conditions studied has not been induced by acid injections up to the present time, or, if already present, it has not been altered by them

7 No evidence has been obtained of hyperesthesia of the gastric mucous membrane, or of pain as the result of hyperchlorhydria with an intact gastric and duodenal mucosa

CHRONIC BILIARY TRACT DISEASE

THE DIAGNOSTIC CRITERIA *

JOHN G MATEER, M D

AND

W STUART HENDERSON, M B

DETROIT

INTRODUCTION

The refinement of gall tract diagnosis in the last decade represents one of the most fascinating pages in the history of modern medicine. The contributions of Lyon,¹ Smithies,² George,³ Graham,⁴ Bernheim,⁵ van den Bergh⁶ and others are particularly noteworthy. Previous to ten years ago, the diagnosis of chronic gall tract disease was almost wholly dependent on clinical acumen in evaluating various symptom complexes and objective physical findings. Even now the clinical findings are of first importance, not only in furnishing evidence of pathologic morphology of the gall tract, but also in affording the indispensable key to a correct functional diagnosis or evaluation of the patients' gastro-intestinal symptoms. At the same time, in the suspected, borderline cases the clinical diagnosis can now be confirmed and further elaborated and refined, by cholecystography, other types of roentgen-ray evidence, transduodenal biliary drainage, and quantitative determination of the serum bilirubin.

This article is based, for the most part, on a careful analysis of the diagnostic data in relation to the pathologic findings in a series of ninety-four consecutive patients with proved gall tract disease who were operated on. In these ninety-four patients the following pathologic con-

¹ Read before the American Congress of Physicians, Detroit, Feb 23, 1926

* From the gastro-intestinal division of the medical department, Henry Ford Hospital

1 Lyon, B B V. Nonsurgical Drainage of the Gall Tract, Philadelphia, Lea and Febiger, 1923

2 Smithies, F, Karshner, C F, and Oleson, R B. Nonsurgical Drainage of the Biliary Tract, J A M A **77** 2036-2043 (Dec 24) 1921

3 George, A W, and Leonard, R D. The Pathological Gallbladder, Annals of Roentgenology, vol 2, New York, Paul B Hoeber, 1922

4 Graham, E A, Cole, W H, and Copher, G H. Roentgenological Visualization of the Gallbladder by the Intravenous Injection of Tetrabromphenolphthalein, Ann Surg **80** 473-477 (Sept) 1924, Cholecystography. Oral Administration of Sodium Tetraiodophenolphthalein, J A M A **85** 953-955 (Sept 26) 1925

5 Bernheim, Alice R. The Icterus Index (A Quantitative Estimation of Bilirubinemia), J A M A **82** 291-295 (Jan 26) 1924

6 Van den Bergh, A A H. La recherche de la bilirubine dans le plasma sanguin par la methode de la reaction diazoique, Presse méd **29** 441-443 (June 4) 1921, abstr, J A M A **77** 235 (July 16) 1921

ditions were found. Forty-one had gallstones, thirty-six (with and without calculi) had chronic cholecystitis with pericystic adhesions, and fifty-three presented chronic cholecystitis without stones or adhesions, thirty-four of the last patients representing early catarrhal cholecystitis.

The majority of the patients having gallbladder studies in this clinic, and presented in this report, are not selected patients referred here for confirmation of diagnosis or operation after the diagnosis of gallbladder disease has been made elsewhere, but rather they represent a fair cross-section of the average variety of patients seen by any internist and many early and borderline cases are included in which the diagnosis of gall tract disease is suspected from the history and physical examination. We have therefore had a favorable opportunity to study the early manifestations of this condition. In this connection it should be emphasized that 36 per cent of the ninety-four patients operated on had *early* chronic cholecystitis.

In order to confirm the accuracy of the patient's history we have, wherever possible, in those cases presenting a history of pain, seen the patient during an attack. However, in the majority it has been necessary to rely on the patient's description of his symptoms. We will devote considerable attention to cholecystography in an effort to aid in the correct evaluation of this new method of diagnosis.

PATHOLOGY

Before considering the diagnostic criteria of chronic gall tract disease, it is important to review the more fundamental facts regarding the pathology of this condition. Although the finding of chronic interstitial hepatitis of varying degrees has been noted by pathologists for many years, its importance as a pathologic and clinical entity has not until recently received the attention deserved. In 1915, Graham⁷ in every case of a series of cases of cholecystitis in which operation was performed, demonstrated some degree of hepatitis. This constant association was essentially confirmed by Judd,⁸ who also noted the frequent association of varying degrees of pancreatitis with chronic cholecystitis. In 1924 Heyd, Killian and MacNeal⁹ demonstrated that varying degrees of hepatitis are associated with appendicitis and peptic ulcer, as well as with cholecystitis and pancreatitis. A piece of liver was excised for microscopic study from patients who were found at operation to have

7 Graham, E. A. Hepatitis, a Constant Accompaniment of Cholecystitis, *Surg Gynec Obst* **26** 521-537 (May) 1918.

8 Judd, E. S. Relation of the Liver and the Pancreas to Infection of the Gallbladder, *J A M A* **77** 197-201 (July 16) 1921.

9 Heyd, C. G., Killian, J., and MacNeal, W. J. The Liver and Its Relation to Chronic Abdominal Infection, *The Beaumont Lectures, Series III*, St. Louis, C. V. Mosby Company, 1924.

cholecystitis, appendicitis, peptic ulcer or other areas of local abdominal infection drained by the portal circulation. By a careful microscopic study of this tissue a tendency toward the development of an acute hepatitis was demonstrated in cases of acute cholecystitis and acute appendicitis. A similar association of chronic hepatitis with chronic gastro-intestinal infections was evidenced by the histologic study of the liver in numerous cases of chronic gallbladder disease, chronic appendicitis and peptic ulcer. In these cases, numerous mononuclear wandering cells were found in the trabeculae of Glisson's capsule, as well as round cell infiltration about the bile ducts, and a definite increase of fibrous tissue within the liver. In many cases this increase of fibrous tissue was evidenced by scarring visible on the exterior of the liver. In certain cases of acute hepatitis, desquamated epithelium and polymorphonuclear cells were seen within the lumen of the intrahepatic bile ducts. Sudler¹⁰ has demonstrated that there are certain lymphatics which carry lymph from the liver to the gallbladder, whereas the direction of flow in a second set of lymphatics is from the gallbladder to the liver. It is therefore anatomically possible for a cholecystitis to develop secondary to chronic infection and inflammation of the liver, and there is much evidence that this is the pathogenesis of chronic cholecystitis in many cases. At the same time, the pathologic studies of Heyd and MacNeal indicate that the various exacerbations of an established chronic cholecystitis tend to produce repeated insults to the liver, resulting in increased hepatic fibrosis. Heyd has noted further that in some cases the hepatitis is quite marked, whereas the degree of gallbladder disease is only slight or moderate. In other cases there is marked involvement of the gallbladder with only a slight hepatitis.

More recently McIndoe and Counsellor,¹¹ at the Mayo Clinic, have shown, by injecting the bile duct systems of livers removed at necropsy from patients with chronic gallbladder disease, that there was marked dilatation of the larger extrahepatic bile ducts. (In this group of cases there was little or no dilatation of the terminal intrahepatic bile ducts.) The contrast with the appearance of the bile duct system in normal cases was quite striking.

The foregoing convincing pathologic evidence that cholecystitis should be regarded only as a part of a generalized, chronic infection and inflammation of the biliary tract has its clinical manifestation in the not infrequent observation that after cholecystectomy there may be symptoms that are definitely traceable to residual cholangitis or hepatitis.

10 Sudler, M. T. The Architecture of the Gallbladder, *Bull. Johns Hopkins Hosp.* 12: 126-129, 1901.

11 McIndoe, A. H., and Counsellor, V. S. Studies in the Vascular and Biliary Trees of the Liver, read before the Pathological Section of the Federation of American Societies for Experimental Biology, Dec. 28, 1925.

HISTORY

The symptomatology of chronic gall tract disease may be considered under four headings. In the first group are included such systemic symptoms as anorexia, asthenia and loss of weight, and these manifestations may be present in varying combinations and degrees. Since such symptoms are associated with numerous other conditions, they are, of course, not diagnostic, but are of value when considered in connection with other symptoms.

Under the second heading are included the symptoms of various conditions, e. g., arthritis, myositis and neuritis, which suggest the presence of chronic infection, but do not directly call attention to the gall tract.

A third group comprises such reflex symptoms as belching, bloating, heartburn, nausea and vomiting. As pointed out by Alvarez¹² and others, these symptoms are dependent on reflex pylorospasm and reverse peristalsis in the gastroduodenal segment. Such types of epigastric distress are, of course, not pathognomonic of chronic gallbladder disease, since they occur also in association with peptic ulcer, chronic irritable colon (chronic colitis), chronic appendicitis and other gastro-intestinal, as well as certain pelvic and urinary tract, conditions. Epigastric distress is, however, the earliest and most frequent gastro-intestinal symptom in chronic gall tract disease. If carefully analyzed, this symptom is, moreover, of some help in differential diagnosis.

Epigastric distress dependent on chronic gall tract disease involves belching and bloating in the great majority of patients, and a type of bloating which is often very distressing, and only partially relieved by carminatives such as soda. Nausea and heartburn are somewhat less frequently present. Epigastric distress referable to gall tract disease is usually differentiated readily from that of peptic ulcer by the following points. In the first place, it develops, as a rule, during the first hour after the intake of food. In other words, with the exception of occasional patients with an ulcer-like history, gallbladder distress is aggravated rather than relieved by food, and is often especially aggravated by fatty foods, e. g., cream, eggs and fried foods. Unlike ulcer distress, that of gallbladder disease also occurs quite irregularly and without any definite periodicity. Gallbladder distress can usually be differentiated from the epigastric distress referable to chronic colitis or chronic irritable colon by the following points. The former is not so constantly or so strikingly aggravated by constipation and relieved by a bowel movement or passing flatus. It also differs from colon distress in that it is not aggravated by cold drinks, has no tendency to occur particularly in the morning, and has no direct relation to the

¹² Alvarez, W. C. *The Mechanics of the Digestive Tract*, New York, Paul B. Hoeber, 1922.

patient's nervous condition. The epigastric distress of chronic appendicitis may simulate closely that of gallbladder disease, but in the latter case there is no history of attacks of right lower quadrant pain.

Under the fourth heading of localizing symptoms, pain under the right costal margin is of first importance. This pain may be dull in character or very severe and colicky. Its frequent radiation to the inferior angle of the right scapula has long been recognized as a helpful diagnostic point when present. Less frequently, the pain may be epigastric in location, and may radiate posteriorly to the interscapular region. In some patients, the periodic attacks of severe pain greatly overshadow the epigastric distress, while in others, the pain may be slight or entirely absent and the epigastric distress may be a most annoying symptom.

The character of the pain present has been analyzed in the series of ninety-four consecutive cases in which operation was performed, and its type noted in relation to the degree and type of gallbladder disease found at operation. In the majority of these cases, as noted above, our information regarding the exact character of the pain is based on the patient's description, being obtained in the interval between attacks.

Gallstones were found in exactly two out of every three patients who characterized their pain as being severe. In those cases having typical colic, with sudden onset of extremely intense pain requiring opiates for relief, gallstones were almost always found at operation, although we have observed several patients with definite colic in whom no calculi were found. Among those who described their pain as dull, gallstones were found in only one patient out of four. The severity of pain, and particularly the presence of typical colic, does, therefore, aid greatly in differentiating the cases with and without stones.

Radiation of pain to the region of the inferior angle of the right scapula was noted in 66 per cent of the group of sixty-one patients who had had pain under the right costal margin and who were operated on. Of the forty patients who had this radiation of pain, 55 per cent showed gallstones at operation. Of the 45 per cent with radiation of pain but no calculi, at operation 53 per cent had pericystic adhesions, whereas the other 47 per cent were patients with simple chronic cholecystitis. In analyzing the group of patients with pain starting in the epigastrium and radiating through to the interscapular region, it was found that exactly 50 per cent presented gallstones at operation, whereas the others harbored no calculi. These findings corroborate the opinion expressed by others that the radiation of pain in chronic gallbladder disease, unlike the severity of the pain, is of no real value in differentiating the patients with and without gallstones or pericystic adhesions.

There are, of course, variations from usual locations and radiations of pain in chronic gallbladder disease mentioned in the foregoing. The

pain may start in the region of the right scapula and radiate forward, or occasionally one sees a person with sharply localized pain referred to a small area beneath the right scapula, and with no radiation. Epigastric pain, instead of radiating to the interscapular region, may shift to the right scapular region or to the right costal margin.

In the differential diagnosis of right upper quadrant pain, one should consider first the more common conditions, such as chronic gallbladder disease and chronic irritable colon, and then the less frequent causes, such as anterior reference of right sided kidney pain, chronic appendicitis involving a displaced, adherent appendix, and the infrequent reference of pancreatic pain to this locality. The fact that chronic irritable colon is a common cause of right upper quadrant pain should be emphasized, as there are frequent errors in the diagnosis of chronic gallbladder disease resulting from the fact that colon conditions are not always given due consideration in this differential diagnosis. Colon pain, fortunately, has numerous features that tend to characterize it as such—for example, its tendency to localize at times in any one of the four abdominal quadrants, but at other times to shift from one quadrant to another, its tendency to be aggravated by coarse vegetables, fruits, cold drinks, constipation and nervous upsets, and to be relieved by fasting or by a bland diet, by the application of heat, by proper regulation of the bowels, or by rest, and finally, by the fact that it usually occurs in transient, cramplike paroxysms, lasting only a short time, whereas in gallbladder attacks the pain may persist rather steadily for a period of several hours.

Twenty-two per cent of the ninety-four cases in which operation was done presented either a definite history of at least one period of jaundice or afforded definite evidence of jaundice at the time of examination, and the history of a periodic "sallow" or "muddy" complexion was frequently elicited. Conversely, in any large group of unselected patients with jaundice, about 55 per cent will be found to have chronic gall tract disease, with either a hepatitis or a stone in the common bile duct as the underlying basis. Determination of the exact cause of jaundice usually involves, in addition to a careful evaluation of the clinical findings, observations on the serum bilirubin, other studies of the blood, examinations of the urine and stool, and duodenobiliary drainage—or at least attempts to obtain bile in this manner. The classical clinical picture in common duct stone of colic, jaundice and evidence of sepsis needs no elaboration.

PHYSICAL EXAMINATION

The evidence of chronic gall tract disease afforded by physical examination must be obtained and interpreted with care, but is of much value. Definite tenderness in the gallbladder region on palpation upward under the right costal margin is a most valuable sign. The importance of differentiating between gallbladder and colon tenderness in the right

upper quadrant should be emphasized. With the patient in the reclining position, this differentiation is frequently difficult or impossible. It is therefore always advisable to examine a patient with suspected gallbladder disease in the sitting posture. This allows the transverse colon to drop down and away from the costal margin, and at the same time facilitates upward palpation of the liver edge and gallbladder region. It is advisable during such examination to have the patient lean slightly forward, breathe through the mouth, and relax the abdominal muscles. The fact that gallbladder and colon conditions frequently coexist adds to the importance of this method of examination. It is a well recognized fact that involuntary increased muscle resistance during palpation is a more reliable indication of significant tenderness than the mere statement of the patient that pain or distress is felt during palpation.

Repeated abdominal examinations during a period of observation are often necessary before gallbladder tenderness is elicited. This fact is, of course, due to the characteristic exacerbations and remissions in the life cycle of chronic gall tract disease. Definite tenderness may be demonstrated in the gallbladder region during or immediately after a gallstone attack, whereas a few hours later it may be impossible to elicit any tenderness in this locality. In 85 per cent of the ninety-four cases in which operation was performed gallbladder tenderness was elicited at one time or another before operation.

The finding of a definite tumor in the gallbladder region, the characteristics of which identify it as the gallbladder, indicates one of four conditions: (1) empyema, (2) hydrops of the gallbladder, usually associated with a stone in the cystic duct, (3) carcinoma, or (4) occasionally, a gallbladder filled with stones which can be palpated through a lax abdominal wall. We have twice seen the latter finding confirmed at operation.

The incidence and evaluation of the finding of jaundice has been discussed under a previous heading.

QUANTITATIVE SERUM BILIRUBIN DETERMINATION

The value of a quantitative serum bilirubin determination in demonstrating a latent jaundice in gall tract disease is now generally recognized. The two methods that are apparently in widest use at the present time are (1) the quantitative *indirect* van den Bergh method,¹³ as modified by Thannhauser and Andersen¹³ and advocated by Greene, Snell and Walters,¹⁴ and (2), the icterus index method as described by

13 Thannhauser, J. S., and Andersen, E. Methodik der quantitativen Bilirubinbestimmung im menschlichen Serum, *Deutsches Arch f klin Med* **137** 179-186 (Aug) 1921, abstr, *J A M A* **77** 1292 (Oct 15) 1921.

14 Greene, C. H., Snell, A. M., and Walters, W. A Survey of Tests for Hepatic Function, *Arch Int Med* **36** 248-272 (Aug 15) 1925.

Beinheim⁵ Because of its simplicity, the latter method has had a rather wide clinical use. It has, however, two important limitations, due to the fact that it is based on the hypothesis that the yellow in the serum is a quantitative index to the amount of bilirubin present. In this connection, Beinheim recognized the necessity of being very careful to avoid any trauma of the red blood cells, which may result in hemolysis with misleading discoloration of the serum. She also recognized the necessity of eliminating from the patient's diet pigment containing foods, such as carrots, which might and do produce discoloration of the serum. If these two pitfalls are kept in mind in using this method, satisfactory results can be obtained in the majority of patients. There can be no doubt, however, that the data obtained will be more uniformly reliable if the quantitative indirect van den Bergh method, which is a specific test for bilirubin, is used. We have frequently used both methods, checking the results of one with those of the other. In addition, the *direct* van den Bergh reaction has been carried out in those cases of clinical jaundice in which there has been some doubt as to the underlying cause or type of jaundice present.

A quantitative serum bilirubin determination is indicated particularly in cases of suspected gall tract disease in which there is still some doubt about the diagnosis after the other diagnostic evidence has been obtained. Such a determination should be carried out, however, in every suspected case of gall tract disease, because it frequently adds to the total diagnosis by affording evidence of hepatitis. Another important use of this procedure consists in the frequent determination of the serum bilirubin during the observation of a frankly jaundiced patient. It is thus possible to obtain early and reliable information as to increase, decrease, or fluctuation in the degree of jaundice, which frequently clarifies the diagnosis of the underlying condition. Furthermore, as emphasized at the Mayo Clinic, valuable information as to the indication for surgical treatment and the best time for operative intervention is obtained in jaundiced cases by following the serum bilirubin until it has reached a stationary level, surgery usually being contraindicated while it is increasing or decreasing.

ROENTGEN-RAY STUDIES

(a) *Earlier Methods*—Until the introduction by Graham of his ingenious method for studying directly the morphology and physiology of the gallbladder, the roentgen-ray methods used in gallbladder diagnosis afforded valuable information in a certain number of cases, but there were too many instances in which they made either no contribution to the diagnosis, or else afforded only evidence of an indirect and inconclusive nature. The two sources³ of roentgen-ray evidence then available were (1) simple gallbladder plates, which in some cases revealed

stone shadows and in others a visible gallbladder shadow, and (2) a barium meal roentgen-ray series, which, in some instances, disclose a concave "pressure defect" (usually involving the duodenal bulb), and in others evidence of right upper quadrant adhesions with displacement and a tendency to fixation of the distal antrum, proximal duodenum or proximal colon

In the indirect roentgen-ray evidence obtained from a barium meal¹⁵ examination, the finding of a definite, concave pressure defect is, we believe, often, although not always, due to gallbladder pressure. We have seen a few patients with a pressure defect who presented at operation a gallbladder firmly attached by adhesions to the first portion of the duodenum, and other patients in whom a cluster of gallstones in the stomach plates nestled in the concavity of a duodenal pressure defect. We are not convinced, however, that pressure of the gallbladder on the duodenum necessarily means cholecystic disease, nor does such pressure, when present, give any indication as to the degree of disease present. Fifty-seven of the ninety-four patients operated on for gall tract disease received a barium meal examination, and 14 per cent (eight cases) presented a persistent concavity involving the first portion of the duodenum. Barium meal evidence of right upper quadrant adhesions, involving the duodenum or proximal colon, is of considerable value when definitely present, although care must be exercised in its evaluation.

The direct evidence obtained from simple gallbladder plates is summarized in table 1. This includes an analysis of the findings in the simple gallbladder plates and cholecystograms of the fifty-eight patients operated on for gall tract disease who were studied by both methods. In this group gallstone shadows were noted in 17.9 per cent of the patients having gallstones at operation. In the total group of ninety-four patients operated on, gallstone shadows were seen in 22 per cent of the gallstone cases. As regards the identification and interpretation of a "visible gallbladder shadow," cholecystography has taught us that in some preliminary gallbladder plates a shadow that apparently represents a gallbladder shadow may be located in a very different position from the known gallbladder shadow in the cholecystograms. We feel, therefore, that, whenever possible, the identification of a "visible gallbladder shadow" should be postponed until the position of the shadow in question can be compared with the known gallbladder shadow in the cholecystograms. If the gallbladder fails to fill with the dye, such comparison is, of course, impossible. In this connection, some shadows can be independently identified as visible gallbladder shadows with somewhat more confidence than others. A visible gallbladder shadow was noted

15 Burnham, M. P. Importance of Indirect Roentgen Findings in Chronic Infection of the Biliary Ducts and Gallbladder, *Am J Roentgenol* 10: 105-112 (Feb.) 1923.

in 10.3 per cent of the fifty-eight pathologic cases. In five of these six cases the position of the shadow coincided with the position of the gallbladder shadow in the cholecystograms. In the sixth case the gallbladder was not visualized in the cholecystograms, but the shadow in the gallbladder plates was quite convincing.

TABLE 1—*Analysis of Cholecystograms and Preliminary Gallbladder Roentgenograms of Sixty-four Patients that Were Operated on*¹

	Number of Cases Presenting Roentgen Ray Sign	Percentage of 58 Pathologic Cases Presenting Roentgen- Ray Sign	Pathologic Findings at Operation, Number of Cases	Percentage of Correct Roentgen- Ray Diagnoses	Percent- age of patients Receiv- ing Dye Orally
I Cholecystograms					
No gallbladder shadow	27	43.1 (25 cases)	(a) Cholecystitis 8 (b) Gallstones 17 (c) No disease 2	92.6	89
Faint gallbladder shadow (with or without asso- ciated mottling of shadows or loss of sequence)	13	20.7 (12 cases)	(a) Cholecystitis 8 (b) Gallstones 1 (c) No disease 1	92.3	77
Stasis (appreciable degree, with only slight con- traction of gallbladder shadow)	1	6.9 (1 case)	(a) Catarrhal cholecystitis 4	100	50
Negative stone shadows	5	8.6 (18% of gallstone cases)	(a) Gallstones 5	100	100
Positive stone shadows† (gallbladder not visual- ized with dye)	4	6.9 (11.3% of gallstone cases)	(a) Gallstones 4	100	100
Irregularity (angular) in contour of gallbladder shadow	9	15.5	(a) Chronic cho- lecystitis with pericystic adhe- sions 8 (b) Gallstones 1	100	89
Normal shadows and sequence	7	6.9 (1 patho- logic cases)	(a) No disease 3 (b) Cholecystitis 3 (c) Gallstones 1†	12.0§	12.9
II Gallbladder roentgenograms					
Gallstone shadows	5	8.6 (17.9% of gallstone cases)	(a) Gallstones 5	100	
Visible gallbladder shadow (described in context)	6	10.3	(a) Cholecystitis 2 (b) Gallstones 1	100	
Total cases with either gallstone shadows or visible gallbladder shadow	9	15.5 (32.1% of gallstone cases)	(a) Cholecystitis 2 (b) Gallstones 7	100	

* Fifty-eight of these patients presented at operation definite evidence of chronic gallbladder disease, twenty-eight having gallstones. The oral method of cholecystography was used in 80 per cent (fifty-one) of these cases.

† Not included under specific cholecystographic evidence, because also obtained from preliminary gallbladder plates.

‡ Although a normal gallbladder shadow was seen in the second set of cholecystograms, no gallbladder shadow was seen in the first cholecystograms of this patient. (The sequence of shadows is therefore not entirely normal in this case.)

§ This percentage figure would doubtless be much higher in a group of cases without definite clinical evidence of cholecystitis.

|| The error involved in those cases with an apparently visible gallbladder shadow, the position of which did not coincide with that of the gallbladder in the cholecystograms, is not included in this figure.

(b) *Cholecystography*—Cholecystography, first presented to the medical profession by Graham in 1924, at present justifies the enthusiasm noted at the time of its introduction. During the last year we have carried out cholecystography in 590 cases of suspected gallbladder disease, and during this time we have been much interested in the evolution of

the method, both as to the dye used and the method of administration. A careful analysis of the patient's reactions following various methods, and also of the findings in the cholecystograms, has afforded interesting results and conclusions.

1 Evolution of Method After carrying out the intravenous administration of sodium tetrabromophenolphthalein in forty-seven cases, this method was entirely discarded because a marked circulatory reaction was obtained in 17 per cent of the patients, with a transient state of collapse in 6 per cent. It should be noted, however, that there were no unfavorable end-results. With the demonstration by Whitaker and Milliken¹⁶ that sodium tetraiodophenolphthalein is no more toxic per unit weight than sodium tetrabromophenolphthalein, and that a smaller quantity of the iodine dye gives equally satisfactory shadows, cholecystography was carried out on seventy patients to whom the iodine rather than the bromine salt was given intravenously. By this change of method, circulatory reactions were reduced from 17 to 14 per cent. Furthermore, 60 per cent of the patients had no reaction of any sort. Several of the latter, however, did develop rather extensive thromboses of the arm veins. In view of this fact, and since any intravenous method is time consuming and necessitates hospitalization of the patient, we have now practically given up the intravenous method. Administration of the dye through the duodenal tube was carried out in a few cases, but was discontinued as soon as it was learned that most of these patients had vomiting, and some circulatory reactions, apparently due to the rapid absorption of the dye. Since the publication of the first oral method by Menees and Robinson,¹⁷ we have administered the dye orally to 463 patients. Menees' method of administering the dye emulsified in olive oil and in gelatin capsules that have been exposed to formaldehyde has proved most satisfactory. Oral administration of the dye in tablets coated with phenol salicylate was discarded because diarrhea occurred three times as frequently as with the gelatin capsules that had been exposed to formaldehyde. With the oral method we have seen no circulatory reactions. In the relatively small group of cases with suggestive but not definite evidence of cholecystic disease in the cholecystograms, and no definite clinical evidence, it seems preferable to repeat the oral method and rely on the constancy of the findings, rather than resort to the intravenous administration for confirmation. Ques-

16 Whitaker, L. R., and Milliken, G. Comparison of Sodium Tetrabromophenolphthalein with Sodium Tetraiodophenolphthalein in Gallbladder Radiography, *Surg Gynec Obst* **40** 17-23 (Jan) 1925.

17 Menees, T. O., and Robinson, H. C. Oral Administration of Sodium Tetrabromophenolphthalein, Preliminary Report, *Am J Roentgenol* **13** 368-369 (April) 1925, Oral Administration of Tetraiodophenolphthalein for Cholecystography, *Radiology* **5** 211-221 (Sept) 1925.

tionable points have thus usually been cleared up in a satisfactory manner. No appreciable difference has been noted in the incidence of local gastro-intestinal disturbances in comparing the eighteen patients who received the bromine salt orally with the 445 patients who were given the iodine salt by mouth. Preference has been accorded the iodine salt because, as noted above, the toxicity of the dose necessary to produce satisfactory shadows is much less than that of the bromine salt.

2 **Present Method of Administration of Dye and Rationale** The oral method followed at the present time and its rationale are as follows. Ten-grain (0.6 Gm.) gelatin capsules are exposed under a bell jar to formaldehyde fumes, as recommended by Menees¹⁷. Exposure for a period of six hours is much more satisfactory than the longer period of twenty-four hours first used. With this change in technic the capsules are more promptly digested in the intestine. The capsules should be freshly exposed to formaldehyde every several days, as old capsules exposed to formaldehyde seem to digest less promptly in the intestine. We have used capsules exposed to formaldehyde rather than those coated with keratin because *in vitro* experiments, in which artificial gastric juice was used, have convinced us that capsules exposed to formaldehyde for six hours were somewhat more resistant to gastric digestion than those with keratin coating. It is important to note that the main objection raised against the oral method is the possibility that the dye capsules may be only partially digested and the dye incompletely absorbed. That this is not a valid practical objection, if a proper technic is used, is apparent from the following facts:

1 The stools of fifty consecutive patients, who had received dye capsules exposed to formaldehyde for six hours, were sieved, all stool specimens having been saved over a period of thirty-six hours after administration of the dye, but not a single undigested capsule was found. (Loss of dye by the vomiting of capsules occurs only rarely, and is readily detected when it does occur, if the patient has been properly instructed.)

2 In a group of cases large serial films taken every hour after oral administration have shown that the dye capsules begin to break down within two hours, and digestion of the capsules is usually complete within eight hours.

3 With the technic now used no undigested capsules have been found in the large films of the abdomen, taken routinely when the twelve hour cholecystograms are obtained, and those cases presenting small quantities of disseminated, unabsorbed dye in these films can be noted in relation to the interpretation of the cholecystograms.

4 As noted below, the entrance of the dye into the gallbladder and the visibility of the gallbladder shadows have been essentially as satis-

factory with the oral as with the intravenous method, although the shadows are, of course, less dense

Into each capsule exposed to formaldehyde 0.5 Gm of sodium tetraiodophenolphthalein is introduced, emulsified in a small quantity of olive oil. The two parts of the capsule are then sealed with melted gelatin. We agree with Stewart¹⁸ that it is important to use a fresh preparation of the dye. As regards the quantity of the iodine salt to be given, 0.06 Gm per kilogram of body weight (with minimum and maximum doses of 2.5 and 5.5 Gm, respectively) has been found to produce satisfactory shadows. With this dose of fresh dye, nausea and vomiting occur in only a small percentage of patients. Rather than give a larger number of smaller capsules in order to maintain more accurately the exact proportion between body weight and amount of dye given, it has been more satisfactory, on the whole, to administer the larger dose per capsule referred to above, and to give from five to eleven capsules in divided doses at 8 and 8.30 p. m., the patient having previously eaten a small meal at 5 p. m. The patient is instructed to retire before taking the capsules. One dram of sodium bicarbonate is given at 8 p. m., and again at 8.30 p. m., in order to prevent precipitation of the dye within the capsule by the entrance of hydrochloric acid.

3 Time Intervals Observed in Taking Cholecystograms On the day following ingestion of the dye, twelve hour plates are taken at 8.30 a. m., sixteen hour plates at 12.30 or 1 p. m., and twenty hour plates at 4.30 p. m. A final set of thirty-six hour plates have been taken at 8.30 a. m. of the following day. After taking the dye capsules the patient fasts until after the sixteenth hour plates are obtained. A small meal, including beef broth and cream, is then given in order to induce as much emptying of the gallbladder as possible before the twenty hour plates are taken. Subsequently, the patient eats the usual evening meal, and breakfast the following morning. Immediately after the twelve hour cholecystograms and the large control plate of the entire abdominal cavity have been taken, the patient is given a cleansing enema in preparation for the sixteen and twenty hour plates. A second enema is given on the morning of the following day preparatory to the thirty-six hour films. As noted below, we feel that there is doubt as to the value and interpretation of the thirty-six hour plates, and we are planning to discontinue them.

4 Signs and Their Evaluation Of the 590 patients studied by cholecystography, sixty-four have, up to date, come to operation and the operative findings have been compared with the evidence in the

¹⁸ Menees and Robinson (footnote 17) second reference, discussion by W. H. Stewart

cholecystograms Fifty-eight of these patients presented definite evidence of chronic gallbladder disease, twenty-eight having gallstones (Of the ninety-four patients operated on for gall tract disease who have been analyzed from the standpoint of clinical findings, the last fifty-eight patients had cholecystography) The gallbladder appeared normal at operation in the other six cases, and was not removed Eighty per cent of the patients operated on received the dye orally, and the results are, therefore, mainly an index to the value of the oral method The incidence and reliability of the various cholecystographic signs in these sixty-four cases are indicated in detail in table 1 By referring to table 2 it will be noted that the positive cholecystographic evidence is considered under the two headings of indirect and direct evidence

The sign which occurs with greatest frequency, and which is more reliable than any of the other indirect signs, is failure to visualize a gallbladder shadow in any of the serial cholecystograms Forty-three per cent (twenty-seven of the sixty-four cases) presented this sign Gallstones were found at operation in 63 per cent (seventeen) of these cases with no visualization of the gallbladder (In one case carcinoma of the gallbladder was found in addition to calculi) Eight of these cases had a cholecystitis without stones, and in two cases the gallbladder appeared normal at operation, and was not removed In the last two cases the operation was performed, in one instance, for pyloric obstruction and in the other for chronic appendicitis, the gallbladder being explored because of the roentgen-ray observations The percentage of correct diagnosis with this sign was therefore 92.6 per cent Twenty-four of the twenty-seven patients presenting this sign received the dye orally Impaired ability of the gallbladder wall to concentrate the solid contents of the bile would seem frequently to be the important factor in the failure of the gallbladder to become visible with the dye In other cases, cystic duct obstruction or obliteration of the gallbladder lumen with calculi is doubtless the cause

A second, less frequent, indirect sign of value consists in persistent faintness of the gallbladder shadow in the serial cholecystograms Although with the oral method the interpretation of faintness of the shadow is not so easy and unequivocal as with the intravenous method nevertheless we agree with the opinion expressed by Carman¹⁹ and others that this sign is of considerable value, provided uniform technic is followed and if the following points are considered in this technic (1) careful notation of any dye lost, (2) consideration of thickness of the patient's abdominal wall, and (3) variation in the dosage of the dye depending on the patient's weight If under these conditions the faint-

19 Carman, R. D. Cholecystography in Its Application to the Diagnosis of Cholecystic Disease, *Minnesota Med* 8 707-712 (Dec.) 1925

ness is definite and marked, and particularly if some other indirect sign, such as delayed visualization of the gallbladder, failure of the shadow to contract, appreciable stasis of the dye or mottling of the shadow, is present, one is justified in attaching diagnostic value to the observation. This sign was present in 20.7 per cent (thirteen) of the sixty-four patients. In 92.3 per cent, or twelve of these patients, some degree of chronic cholecystitis (with or without stones) was found. In ten of these thirteen patients there was not only faint filling but also definite mottling of the gallbladder shadow, which did not give the impression of superimposed gas in the intestine. In ten of the thirteen patients the oral method was used.

The third indirect sign consists of delayed emptying of the gallbladder, which, when marked, and particularly when associated with only slight contraction of the shadow, is of very suggestive diagnostic value. If, on the other hand, there is good contractility of the shadow and only a relatively small amount of dye is visualized in the third set of cholecystograms, one is not justified in attaching any definite significance to the observation. As regards the interpretation of the thirty-six hour plates in relation to stasis, reabsorption of the dye constitutes a possible source of error. We have noted several cases in which the gallbladder shadow had entirely disappeared in the twenty-four hour plates, but was readily visualized again in the thirty-six hour films. Four of the cases in which operation was performed presented marked stasis of the dye with only slight contraction of the shadow, and in all of these a catarrhal cholecystitis was found at operation. Appreciable stasis of the dye has been noted in a much larger number of cases that have not come to operation. A study of further operated cases is necessary before this sign can be satisfactorily evaluated. The fourth indirect sign, *delayed* filling or visualization of the gallbladder, also deserves further study as to its value.

There are two *direct* signs in cholecystography which are of definite diagnostic value when present, viz., (1) negative gallstone shadows, and (2) angular irregularity in the contour of the gallbladder shadow. A total of 24.1 per cent (fourteen) of the fifty-eight pathologic cases presented definite evidence of one or the other of these two direct signs. In 8.6 per cent of these cases in which operation was done, and in a larger number of cases in which operation was not yet performed, areas of negative density were noted within the gallbladder shadow, the character of which definitely identified them as gallstone shadows. In none of these cases were gallstone shadows apparent in the preliminary gallbladder plates. On the other hand, the heavier, calcified type of stone, which reveals itself in the simple gallbladder plates, may be entirely concealed in the cholecystograms if the dye enters the gallbladder and is

concentrated In four of the five cases in this series which showed positive gallstone shadows in the preliminary gallbladder plates, the gallbladder failed to fill with the dye and the positive stone shadows therefore persisted in the cholecystograms (tables 1 and 2)

Angular irregularity in the contour of the gallbladder shadow may be considered under two headings In four of the cases in which operation was performed there was, in the cholecystograms, a striking and persistent displacement of the lower pole of the gallbladder This involved a marked and angular flexion of the fundus on the neck of the viscus In all four cases the preoperative diagnosis of pericystic

TABLE 2—*Deductions from Table 1*

	Total Number of Cases	Cases Presenting Gallbladder Disease	Cases With No Disease at Operation	Percentage of Correct Diagnoses	Percentage of Error in Diagnosis
Cases presenting positive (direct or indirect) evidence with cholecystography	57	54	3	94.7	5.3
Cases presenting normal shadows with cholecystography	7	4	3	42.9 *	57.1
Total cases in which operation was performed studied by cholecystography	64	58	6	89.1 (57 cases) (positive and negative diagnosis)	10.9 (positive and neg ative error) 4.7 (3 of 64 cases)
Percentage of positive error in diagnosis by cholecystography in total cases studied					6.2 (4 of 64 cases)
Percentage of negative error in diagnosis by cholecystography in total cases studied					
	Total Number of Cases	Percentage of Total (58) Pathologic Cases			
Pathologic cases with direct evidence in cholecystograms of chronic gallbladder disease, and no evidence in preliminary gallbladder roentgenograms	14	24.1			
Pathologic cases with either direct evidence or persistent absence of shadow, and no evidence in preliminary gallbladder plates	30 (16 "no shadow" cases)	51.7			
Pathologic cases with some type of direct or indirect evidence of disease in cholecystograms (table 1) and no evidence in preliminary gallbladder roentgenograms	45	77.6			

* This percentage figure would doubtless be much higher in a group of cases without definite clinical evidence of cholecystitis

adhesions was confirmed at operation It seems likely that further experience will confirm the reliability of this sign This type of angular deviation in the long axis of the gallbladder should be differentiated from the rather frequent lateral or medial displacement without angular deviation The latter finding has no definite pathologic significance

In five of the cases in which operation was performed an irregularity in the gallbladder contour was noted, without any deviation of its long axis In four of these five cases dense pericystic adhesions were found, without gallstones In the fifth case gallstones were found, without pericystic adhesions

To summarize, eight of the nine cases with irregular contour of the gallbladder shadow presented pericystic adhesions as the cause of this

finding, whereas the ninth patient had gallstones. This sign was present in 30 per cent of the patients who showed pericystic adhesions at operation.

It is finally important to determine the significance of entirely normal findings in the cholecystograms. Do such findings have a value in ruling out cholecystic disease? Seven patients were operated on whose cholecystograms indicated normal filling, emptying, density and contour, except that one case showed evidence of delayed filling or visualization of the gallbladder. Four of these patients had convincing clinical evidence of cholecystic disease. Three of these four patients were found at operation to have a catarrhal cholecystitis, and the fourth patient (with delayed filling, but a normal shadow) had gallstones. All were relieved of symptoms following cholecystectomy. These cases prove definitely that normal observations with cholecystography do not rule out chronic gallbladder disease, and should not be accorded negative value in the presence of positive clinical data. Normal cholecystograms, however, make unlikely the presence of marked gallbladder disease and necessitate convincing clinical evidence to justify a definite diagnosis of cholecystitis. Other writers have reported but few cases of gallstones or marked thickening of the gallbladder wall at operation associated with normal cholecystography. In view of the fact that very early cases of chronic cholecystitis may show only slight deviation from normal in the physiology and gross anatomy of the gallbladder, and may yet present convincing clinical evidence of disease, it seems probable that this group of cases will constitute the most important limitation of cholecystography. It seems probable, however, that by giving more consideration to the concentrating function of the gallbladder, as evidenced by the indirect cholecystographic signs and the sequence of the shadows, that a larger percentage of comparatively early cases of cholecystitis will be diagnosed by this method. The other three patients operated on who had normal cholecystograms had no clinical evidence of gallbladder disease, and were operated on for some other abdominal condition. These three gallbladders appeared normal.

In summarizing the value of cholecystography, it is noted that this method afforded correct evidence as to the presence of chronic gallbladder disease in 89.1 per cent of this group of sixty-four cases in which operation was performed (table 2). The percentage of positive error in diagnosis was 4.7, whereas the negative error was 6.2 per cent.

In estimating the value of cholecystography as an additional aid to the roentgen-ray diagnosis of gallbladder disease, it is interesting to note that, of the fifty-eight pathologic cases, 51.7 per cent failed to show evidence of gallbladder disease in the preliminary gallbladder plates, and yet showed either direct cholecystographic evidence or persistent

failure of the gallbladder to be visualized in the cholecystograms. This percentage of cases is further increased if all cholecystographic evidence is included.

Late review of a larger group of cases in which operation was performed may reduce somewhat the percentage of correct diagnosis with this method, but there can be no doubt that the percentage will still be high. It will be interesting to obtain an operative check on cholecystography which will include a larger number of borderline cases that lack convincing clinical evidence of gallbladder disease. It will be in this group of cases that cholecystography will receive the most severe test as to its limitations.

DUODENOBILIARY DRAINAGE

Since the introduction by Lyon¹ of duodenobiliary drainage as a method of value in gall tract diagnosis, it has been employed extensively as a diagnostic measure, and also as a therapeutic measure in selected cases. As a result, much has been learned about its value and limitations. The technic of the method is well known to all. The importance of prompt examination of the bile specimens is also now generally appreciated.

Rather than enter on a discussion of some of the points which are still controversial, we wish to direct attention to the conclusions arrived at concerning its practical value and limitations, and to the observations on which these conclusions are based. This consideration will be limited mainly to the significance of three microscopic findings in the bile: (1) bile stained clumps of pus cells, (2) bile stained colonies of bacteria, and (3) cholesterol or calcium crystals.

In the interpretation of these cytologic elements found in the bile obtained from the duodenum, it has seemed important, in the first place, to determine whether in each individual case the material might have come from the mouth, stomach or duodenum, second, whether the evidence indicates that it does come from some part of the bile tract, and if so, in the third place, whether it originates from the gallbladder or from some part of the bile duct system.

Anyone who has examined many bile specimens from patients with suspected gall tract disease will appreciate the fact that small mucous flecks containing bile stained pus cells are frequently found. The importance of determining the point of origin of these cells depends on the recognized fact that pus cells indicate irritation and inflammation at the site of their liberation. The possibility of focal infection in the mouth, nose or throat, or of infection of the gastric mucosa, has been considered in each case as a possible source for the pus cells found in the bile. In other words, it is conceivable that pus cells may enter the duodenum from the stomach, and there become bile stained.

That neither the mouth, stomach nor duodenum are the usual source of the bile stained pus cells found in the recovered bile is evidenced by the following facts. In the first place, it is recognized that the pus cells in the fasting gastric contents are very frequently associated with squamous mouth epithelium, and have originated from focal infection in the mouth, nose and throat. In view of this fact, if the pus cells that originate in the mouth and throat and pass into the stomach were the common source for the pus cells found in the bile, we should expect to find the same association of squamous mouth epithelium with the pus cells in the bile as with those found in the stomach. This is certainly not the case. In fact, squamous epithelium is rarely found in the microscopic examination of either the bile or duodenal contents. It is evidently digested for the most part in the stomach, along with at least many of the pus cells. The type of epithelium that does occur rather frequently in the bile, and in association with the bile stained pus cells, consists of the fans of characteristic, high columnar bile duct epithelium described by Lyon. The fact that the shape and size, as well as the position of the nuclei, of these cells are quite different from the morphology of gastric epithelium, and also different from duodenal epithelium, is a convincing argument against the hypothesis that the pus cells found in the bile originate in the stomach or duodenum.

In the second place, one frequently fails to find pus cells in the control fasting gastric contents, in the washings from the stomach, or in the duodenal contents, and yet may find an abundance of bile stained pus cells in two or three consecutive bile specimens. Conversely, one frequently finds numerous pus cells in the fasting gastric contents, and yet no pus cells in the duodenal contents or in any of the bile specimens. In other words, there is no constant tendency to coexistence of pus cells in the gastric contents and pus cells in the duodenal contents or bile.

In the third place, bile stained pus cells were found before operation in the bile of 51 per cent of our series of ninety-seven cases of chronic gall tract disease in which operation was performed whereas pus cells were found in the duodenal contents in only 10 per cent of the same group.

Other observations could be cited to support the belief that the bile stained pus cells originate, at least in many cases, from some part of the biliary tract. Specimens of bile which contain an admixture of gastric contents, and in which the interpretation of the microscopic findings should be particularly critical, are easily identified, as a rule, by the turbid layers of bile salts, precipitated by spurts of acid gastric juice. As a safeguard against error of interpretation in the individual case, a microscopic examination of the fasting gastric and duodenal

contents should always be carried out as a control for the interpretation of the bile examination

Although the significance of the bile cultures is still a matter of controversy, the microscopic observation of numerous, bile stained colonies of bacteria in the bile of patients whose gastric and duodenal contents fail to show bacteria constitutes quite convincing evidence of gall tract infection. *Colonization* of bile stained bacteria, as emphasized by Lyon, points to the actual growth and multiplication of organisms rather than simply to bacteria in transit

In those cases which present convincing evidence that the bile stained pus cells or colonies of bacteria originate from some part of the biliary tract, we have been interested in determining whether this evidence of inflammation and infection comes from the gallbladder or from some part of the bile duct system. Bile has been aspirated directly from the gallbladder of fifty-four of the ninety-four patients with chronic gall tract disease operated on, and has been examined microscopically. No pus cells or epithelium were found in any of these specimens. This we regard as convincing evidence that the bile stained pus cells previously found in the duodenal bile of 51 per cent of the same group did not come from the gallbladder, but rather from some part of the biliary duct system. This observation also suggests that these bile stained pus cells are probably contributed to the bile as it passes through the lower part of the common bile duct, rather than that they originate in the smaller ducts. For, if the latter were true, one would expect to find bile stained pus cells in the gallbladder bile at operation. To summarize. The observation in the bile of bile stained pus cells and bile stained colonies of bacteria, when other sources have been excluded, affords direct evidence of a chronic cholangitis (probably involving the common bile duct) and indirect evidence of some degree of cholecystitis.

The other important microscopic observation in the bile is the observation of cholesterol or calcium crystals. Lyon,¹ Einhorn²⁰ and Jones²¹ have emphasized the value of this observation in the bile in the diagnosis of gallstones. Of the fifty-four cases of chronic gall tract disease in which operation was done and the gallbladder bile examined at the time of cholecystectomy, and the results compared with those of the duodenal bile, twenty-three patients had stones in the gallbladder. The gallbladder bile of these patients revealed an abundance of cholesterol crystals in seventeen cases, or 74 per cent. In many of

²⁰ Einhorn, M. The Importance of the Direct Examination of Bile in the Diagnosis of Gallbladder Lesions, *M. J. & Record* **120** 9-13 (July 2) 1924, **120** 60-62 (July 16) 1924

²¹ Jones, C. M. The Rational Use of Duodenal Drainage, *Arch. Int. Med.* **34** 60-78 (July 15) 1924

these cases the crystals were clumped. One sixth of these gallbladder biles contained associated calcium crystals. Of the seventeen gallstones cases showing cholesterol crystals in the gallbladder bile at operation, in 35 per cent an appreciable number of these crystals (often clumped) were found in the duodenal bile before operation. This percentage would probably have been higher if the bile had been centrifugalized in every case. The presence of crystals in the duodenal bile does not, however, necessarily mean gallstones, since the former were found in the duodenal bile of 16 per cent of the gallbladder patients who presented no calculi at operation. However, where showers of crystals, including clumps, are found in the duodenal bile, gallstones will be found at operation in the majority of cases. In fact such clumps are miniature stones.

SUMMARY

This study is mainly based on a detailed analysis of the diagnostic findings in ninety-four consecutive operated patients with chronic gall tract disease.

Recent pathologic studies indicate that chronic gall tract disease involves not only a chronic cholecystitis but also a chronic interstitial hepatitis and a chronic cholangitis with dilatation of the larger extra-hepatic bile ducts. The relative degree of involvement of the gallbladder, bile ducts and liver varies greatly in the individual case, making it desirable to use various methods of diagnosis to obtain information regarding the involvement of these three parts of the biliary tree.

The history, when carefully taken, affords most valuable evidence for the presence of gall tract disease. Furthermore, it is indispensable to a correct functional diagnosis and a proper evaluation of the gastrointestinal symptoms. This is especially important in patients who have evidence of several pathologic conditions in the gastro-intestinal tract.

The physical examination aids greatly in the differential diagnosis of gall tract disease from chronic irritable colon, chronic appendicitis, renal disease and other less common conditions.

Graham's contribution, cholecystography, affords reliable information about the gallbladder in a high percentage of cases, and has greatly refined gallbladder diagnosis. The oral administration of the dye is unobjectionable, and also reliable, if a proper and uniform technic is followed. In those cases presenting suggestive evidence of gallbladder disease in the cholecystograms, without definite clinical evidence, we prefer to repeat the oral method rather than resort to intravenous administration. Other roentgen-ray methods are still of value in a smaller percentage of cases, and should be used in conjunction with cholecystography.

Duodenobiliary drainage affords important direct evidence of chronic cholangitis, and valuable indirect evidence of cholecystitis, in the finding of bile stained clumps of pus cells and bile stained colonies of bacteria, frequently in association with bile duct epithelium. Showers of clumped crystals in the bile strongly suggest gallstones.

By utilizing biliary drainage to determine the earliest stages of bile duct infection and inflammation, cholecystography to ascertain the pathologic physiology and anatomy of the gallbladder, and a serum bilirubin determination to gain some idea relative to the liver involvement, the diagnosis of early gall tract disease, suspected on the basis of clinical symptoms, can now be confirmed and refined.

As in other fields of diagnosis, a close correlation of the data obtained from various sources is of utmost importance.

THE RELATION OF MENSTRUATION TO THE PERMEABILITY OF THE SKIN CAPILLARIES AND THE AUTONOMIC TONUS OF THE SKIN VESSELS *

WILLIAM F PETERSEN, M D

AND

GEORGE MILLES, S B

CHICAGO

In view of the intimate relation of the capillary permeability to autonomic and endocrine disturbances and the peculiar effect apparent in the reactivity of the skin, we have carried out a series of blister observations on a group of normal young women. The technic has been that described in the first article ¹

That there is a change in capillary permeability preceding and during menstruation has been determined by Heilig and Hoff ² and by Benda, ³ who have worked with dye injections and have found that the meninges becomes more permeable. Heilig and Hoff found in animal experimentation that thyroid extract and ovarian extract make the meninges more permeable ⁴

In the accompanying table we have tabulated the blister time and the permeability ratio in relation to the menstrual time. In the first part (*A*), menstrual and premenstrual observations show that in the premenstrual period the blister time is shortened (the skin is parasympathetic, the internal organs relatively sympathetic), with the onset of menstruation the skin becomes sympathetically oriented (the internal organs parasympathetic)

In the second part (*B*) the intermenstrual cases have been recorded, with a blister time that is a little longer than the menstrual and an average permeability ratio of 0.72, as compared to the premenstrual of 0.75 and the menstrual of 0.77

These time relationships have been graphically shown in the accompanying chart

* From the department of pathology, University of Illinois College of Medicine

1 Petersen, W F, and Willis, D A. Capillary Permeability and the "Inflammatory Index" of the Skin and in the Normal Person as Determined by the Blister, *Arch Int Med* **38** 663 (Nov) 1926

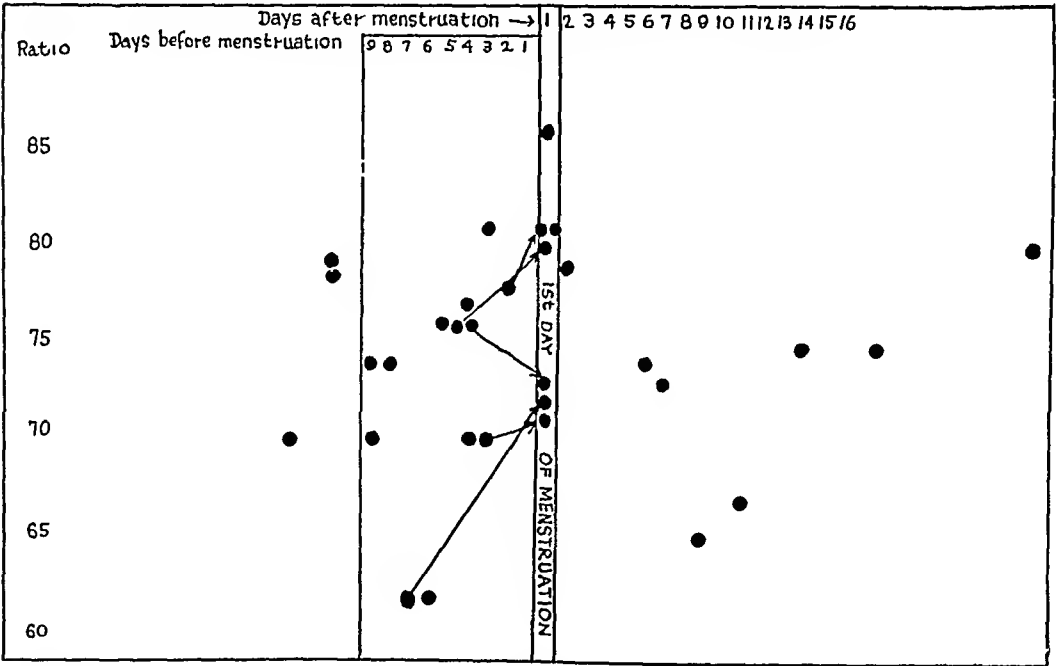
2 Heilig, R, and Hoff, H. *Klin Wchnschr* **3** 2049 (Nov 4) 1924

3 Benda, Robert. *Munchen med Wchnschr* **72** 1686 (Oct 2) 1925

4 Schrader (Mitt a d Grenzgeb d Med u Chir **34** 260, 1921) has approached the problem in another way. By means of local constriction he was able to determine that capillary hemorrhages took place readily in the skin in women from two to eight days before menstruation but ceased at once with the onset of menstruation

Relation of Menstruation to Capillary Permeability, Blister Time and Blood Pressure

Time Relation to Menstruation	Blister Time		Protein		Permeability Ratio		Blood Pressure	
	Before Menstruation Hours	During Menstruation Hours	In Serum, per Cent	In Blister, per Cent	Before Menstruation	During Menstruation	Sys-tolic	Dias-tolic
A								
Menstrual and Premenstrual								
6 Two days before Second day of menstruation	3		7 10	5 6	0 78		126	75
		5	8 04	6 566		0 81		
17 Three days before First day of menstruation	8		7 416	5 294	0 71		122	75
		7½	7 73	5 11		0 70		
10 Four days before First day of menstruation	1½		7 85	6 00	0 76		122	80
		6	8 064	5 9		0 73		
9 Five days before First day of menstruation	3½		8 28	6 304	0 76		120	65
		5	8 064	6 5		0 80		
22 Seven days before First day of menstruation	4		8 28	5 294	0 62		100	71
		4½	7 95	5 9		0 74		
Menstrual								
S81 First day of menstruation		5½	6 77	5 9		0 86		
4 Second day of menstruation		5	7 416	5 9		0 79		
Premenstrual								
1 Five hours before onset of menstruation	3		8 28	6 708	0 81		108	80
2 Three days before	4		8 28	6 708	0 81		110	65
8 Four days before	3		7 85	6 00	0 77		110	70
18 Four days before	4		7 85	5 493	0 70		105	70
3 Five days before	3		8 28	6 64	0 80		130	60
7 Five days before	3½		7 85	6 102	0 76		138	80
Average	3 6	5 5			0 75	0 77	117	72
B								
Intermenstrual								
5 Eleven days before	8		7 416	5 9	0 79		108	60
25 Eleven days before	4½		7 73	6 160	0 79		118	68
11 Eighteen days after	3		7 85	5 90	0 75		110	65
12 Fourteen days after	5		7 20	5 40	0 75		112	68
13 Nine days before	2		7 95	5 90	0 74		112	80
14 Eight days before	4		7 63	5 69	0 74		110	70
15 Six days after	3		7 85	5 82	0 74		90	60
16 Seven days after	8		7 632	5 6	0 73		102	75
24 Nine days before	3½		9 02	6 30	0 70		114	70
19 Thirteen days before	7½		8 06	5 695	0 70		108	68
20 Eleven days after	6		8 40	5 695	0 67		128	68
21 Nine days after	4½		8 06	5 294	0 65		118	75
23 Nineteen days after	7		7 85	4 89	0 62		98	70
Average		5 8				0 72	110	69



Relation of permeability to period of menstruation The black dots represent individual readings, when two determinations were made they were connected by a line

Blood pressure examination has given the following results

The average for the intermenstrual group was 110 systolic, 69 diastolic (thirteen examinations), while the premenstrual group averaged 117 systolic, 72 diastolic (eleven cases)

We were unable, in this relatively small group, to determine any relation of the permeability ratio to the incidence to influenza nor could we, in the absence of a complete examination, investigate the relation to tuberculous infection. It was of interest to note, however, that the young woman with the lowest ratio gave the most marked tuberculin reaction. In a general way, the intermenstrual cases all gave a more marked tuberculin reaction than the menstrual and premenstrual. The details will be published elsewhere

COMMENT

In recent years a number of investigators have developed experimental evidence indicating that during the menstrual cycle an autonomic unbalance exists which begins approximately one week before the onset of menstruation and disappears in from three to six days after the beginning of menstruation

Guillaume and Godel⁵ contend that in menstruation we deal with an alternating preponderance of vagus and sympathetic tonus, the former beginning about a week before the onset and then alternating with a sympathetic tonus until about four days before the discharge

Ludlum and McDonald⁶ regard the phenomenon as wholly parasympathetic. They consider that a wave of vagus predominance begins from eight to two days before menstruation, at which time it reaches its maximum. Part of the effect, they believe, is due to the calcium in the blood after it has been liberated from the cells. That actual changes take place in the calcium has been demonstrated by Malamud,⁷ who found that in 57 per cent of women examined during menstruation the calcium content of the serum was increased, in 14 per cent diminished

Unfortunately no parallel potassium titrations were made. Callenberg⁸ found the calcium level of the serum increased during menstrual urticaria and Andersen⁹ finds the calcium content of the serum increased by approximately 1 mg. in the menstrual period

It is obvious that many of the clinical observations of menstruation are indicative of an autonomic alteration. Moore and Cooper¹⁰ inter-

5 Guillaume, A. C., and Godel, R. *Comp. rend. Soc. de biol.* **90** 666 (March 21) 1924

6 Ludlum, S. D., and McDonald, E. *Surg. Gynec. Obst.* **41** 569 (Nov) 1925

7 Malamud, T. *Compt. rend. Soc. de biol.* **91** 26 (June 13) 1924

8 Callenberg, J. *Klin. Wchnschr.* **3** 533, 1924

9 Andersen, W. T. *Hospitaltid.* **68** 1177 (Dec.) 1925

10 Moore, L. M., and Cooper, C. R. *Am. J. Physiol.* **64** 416 (May) 1923

prietary the lowering of the pulse rate as parasympathetic in origin. The exaggerated motility and secretion of the stomach to which Hess and Faltitscheks¹¹ call attention is associated by them with the hyperirritability of the parasympathetic system, which they believe is due to an increased cholin production during menstruation.

We should like to call attention to one important source of confusion when the autonomic status of the organism is discussed, namely, the fact that the skin and periphery is under ordinary circumstances *oppositely* oriented from the splanchnic area.¹² Thus if the tonus of the skin shows an increase sympathetic, the splanchnic area will show an increase of the vagus tonus. To speak merely of a vagotonia during menstruation means relatively little unless we specify what general region of the body is under consideration.

We have been particularly interested in the determination of a possible change in capillary permeability during menstruation because of the direct influence of the menstrual cycle on a number of pathologic conditions.

It is daily gynecologic experience to find an activation of pelvic inflammation or the flare up of a pyelitis during menstruation, in medicine we may observe vicarious bleeding, an occasional icterus, migraine or even meningismus, as well as disturbances of the neurovascular apparatus, the dermatologist sees changes in skin reactivity, the rhinologist observes the menstrual rhinitis, the neurologist, the activation of a psychosis.¹³

Our own interest has centered chiefly on the effect in tuberculosis. From clinical experience it is known that the menstruating tuberculous woman shows evidence of focal activation as well as increased constitutional effects. Indeed, the effect on the temperature is so important that having ruled out pelvic inflammation and pyelitis, a menstrual temperature increase is to be regarded as indicative of some relatively active tuberculous process. Kraus¹⁴ has entered into a discussion of the phenomena and illustrates different types of reactions.

Here, then, we have a clear cut condition of biologic rearrangement whereby the organism becomes less resistant to the infection. Knowing these factors might lead us to an understanding of conditions that favor resistance to infection.

11 Hess, L., and Faltitschek, J. *Wien Klin Wchnschr* **38** 427 (April 16) 1925.

12 Muller, E. F., and Petersen, W. F. *Klin Wchnschr* **5** 2, 1926.

13 Hoff (*Deutsches Arch f klin Med* **150** 1-2, 1926) has, for example, just published a series of latent cerebral conditions made manifest at the time of menstruation. He explains these on the basis of the increased permeability of the meninges, and on the increase in blood pressure in the premenstrual period.

14 Kraus, H. *Wien med Wchnschr* **4** 610, 1905.

We have demonstrated that at the onset of the premenstrual period the capillaries become more permeable and that changes take place in the autonomic innervation of the arterioles whereby the skin region becomes parasympathetic and the visceral area presumably sympathetic. There may be a slight increase of the metabolic rate at this time, although the evidence is conflicting (thyroid hyperfunction). If so, it will have no effect on the temperature of the normal woman because the skin can readily dissipate heat.

If, however, we have somewhere a tuberculous focus, the increase in permeability will have an effect quite comparable to a tuberculin injection, for the exchange of material to and from the focus is accelerated. Tuberculin is liberated from the tuberculous area. If the reaction at the focus is marked, local evidences of the activation may be obtained on physical examination.

The activation may become apparent in the premenstrual period by an increase in the temperature, or may appear as only a transient phenomenon as a temperature increase on the first day of menstruation. The first day or days seem to be particularly favorable for a rise in temperature because of the curious autonomic rearrangement whereby the skin tonus returns to the normal after having been vagotonic during the premenstrual time. The dissipation of heat would, therefore, be less rapid than before.

When we speak of the capillary permeability it should be kept in mind that the changes that we see in the capillary apparently apply to many of the other cellular elements, which probably become more permeable and are stimulated during the menstrual cycle. The increase in blood calcium must mean that tissue calcium is lessened, and presumably the tissue potassium will be found increased. These changes are not necessarily autonomic in the sense that we deal with changes induced by nerve impulses through the autonomic nervous system. They should be termed vegetative, and are induced by changes in ion equilibrium with coincident changes in the endocrine and autonomic nervous control. We would stress this point because much of the tissue that has to do directly with the resistance to the tubercle probably has no direct connection with the autonomic nervous system, or if so, in only a relatively negligible way. The change must take place through the more primitive ionic and hormonal routes.

Confusion exists because many of the agents that we commonly regard as autonomic stimulants *par excellence* really act directly on the cell membrane, irrespective of the nerve ending. Thus pituitary extract and epinephrine make cells less permeable in very high dilution, putting the cell actually into the rest phase, while the same agents may *stimulate*, through their effect on the autonomic ending, certain other cells, such as smooth musculature. Obviously, the specialized effect has been

superimposed on the more primitive and general protoplasmic effect, and yet it is the specialized effect that is commonly studied and regarded as of greatest importance

Generally the agents that stimulate tissues (greater permeability) when acting directly on the cell membrane act parasympathetically—pilocarpine, thyroxin, cholin, muscarin, paraphenylendiamine—on the autonomic apparatus, while pituitary extract, epinephrine, calcium and insulin act in rendering the cell membrane less permeable when directly in contact with it, and sympathetically in reference to the autonomic nervous apparatus. But the autonomic nervous impulse in acting on the cell initiates a reaction (toward rest or toward activity) only in the direction that is determined by the ionic equilibrium of the membrane at the moment the impulse is received. A similar condition is probably true for the effect of the hormones, which must also use the ions as tools with which they may effect changes in cellular activity.

Menstruation represents a biologic rearrangement evidently involving an ionic change, an endocrine change, as well as an alteration in the autonomic nervous apparatus. The three forming the vegetative control of the tissues are the fundamental factors in the reaction of the organism to an infection. In menstruation the alteration, associated with an increased permeability of the capillaries and tissues, makes for less favorable conditions of resistance to tuberculosis. If we use the term vagotonia in the broad sense outlined above, we can term the menstrual cycle as one of vagotonia, and definitely associate this alteration as unfavorable for resistance to tuberculosis. We shall present other evidence supporting this view in further articles.

SUMMARY

Examination by means of the blister method has shown that the normal rate of permeability for skin capillaries is approximately 0.72 for the intermenstrual period, 0.75 for the premenstrual, and 0.77 for the menstrual period.

In the premenstrual period the skin tonus is parasympathetic, this seems to be promptly reversed with the onset of menstruation.

In the premenstrual and menstrual period the blood pressure average is higher than during the intermenstrual period.

The relation of these alterations to tuberculosis resistance is discussed.

HYPERTHYROIDISM, MYXEDEMA AND DIABETES *

RUSSELL M WILDER, M D

ROCHESTER, MINN

Many of the hypotheses concerning the rôle of the thyroid in carbohydrate metabolism have been based on observation of glycosuria in cases of hyperthyroidism and on the study of cases of frank diabetes, associated with diseases of the thyroid

The literature contains a great number of references to evanescent glycosuria and hyperglycemia in patients with toxic goiter. These are common but by no means constant phenomena. After a test meal of 50 or 100 Gm of glucose the blood sugar in such patients may rise to a higher level than is normal, and during the course of three or four hours a few grams of sugar, rarely more, may be excreted. At other times, even with restriction of the diet, there may be traces of sugar in the urine. The intravenous injection of glucose at uniform rates¹ has revealed that, whereas normal persons can be injected intravenously with glucose at a rate of 0.8 Gm for each kilogram of body weight each hour without manifesting glycosuria, patients with hyperthyroidism may excrete sugar at injection rates of 0.6 or even 0.5 Gm an hour for each kilogram. All such observations show that in hyperthyroidism the rate at which the body can assimilate glucose may be disturbed, they do not prove that anything is at fault with oxidation or reduction. Therefore, they do not indicate the existence of diabetes.

There is indeed good evidence to show that the utilization of carbohydrate is actually accelerated by hyperthyroidism in patients who do not have true diabetes. Following test meals of glucose in patients with exophthalmic goiter, as DuBois² and also Sanger and Hun³ have shown, the respiratory quotients rise more abruptly than is normal. This observation has been repeatedly confirmed in this clinic. Whether it means rapid burning of carbohydrate or rapid reduction to fat may be debatable, but there can be no questioning the conclusion that it signifies a normal, or better than normal, utilization. In patients with frank

* From the Division of Medicine, Mayo Clinic

* Read before the Association of American Physicians, Atlantic City, May 5, 1926

1 Wilder, R. M., and Sansum, W. D. d-Glucose Tolerance in Health and Disease, *Arch Int Med* **19** 311-334 (Feb) 1917

2 DuBois, E. F. Metabolism in Exophthalmic Goiter, *Arch Int Med* **17** 915-964 (June) 1916

3 Sanger, B. J., and Hun, E. G. The Glucose Mobilization Rate in Hyperthyroidism, *Arch Int Med* **30** 397-406 (Sept) 1922

diabetes the respiratory quotients are either sluggish or, if the diabetes is extreme, unchanged after the ingestion of sugar. It would seem, therefore, that while hyperthyroidism may, under certain conditions, alter the amount of sugar stored in the body, it can have no diabetogenic action. It is a looser use of the term "metabolism" to include under it such conceptions as absorption and storage, processes which do not involve oxidations or reductions of food materials. But only in this looser sense can there be said to be any proved alteration of carbohydrate metabolism in the great majority of patients with hyperthyroidism.

The literature contains far fewer frequent reports on cases of frank diabetes complicating hyperthyroidism, and the deductions regarding the significance of these rest as a rule on material that is too limited or too incompletely controlled to make them conclusive.

The present study is confined to the consideration of frank diabetes and is not concerned with transient or alimentary glycosuria. It involves an analysis of thirty-eight cases of persistent glycosuria (diabetes), fifteen in patients with exophthalmic goiter, twenty-three in patients with adenomatous goiter with hyperthyroidism, and one case of diabetes associated with myxedema. The differentiation of toxic goiter into adenomatous goiter with hyperthyroidism and exophthalmic goiter follows H. S. Plummer's classification.⁴ In a preliminary report⁵ based on a detailed study of the metabolism in four of these cases, the clinical importance of recognizing exophthalmic goiter in diabetes was emphasized and the following conclusions were drawn. The exophthalmic goiter syndrome reduces the ability of the diabetic patient to utilize carbohydrate, decreases the efficiency of the unit of insulin, increases the danger of sudden onset of diabetic coma, and the control of this syndrome by the administration of iodine markedly improves the carbohydrate tolerance. The evidence now submitted not only supports these conclusions but permits of their extension. In all of the cases here reported the diagnosis of hyperthyroidism has been confirmed by observation of the basal metabolic rate. In the operative cases, numbering thirty-two, the pathologic examination of the removed thyroid tissue is available. In fourteen of the patients with exophthalmic goiter the effect of the administration of iodine has been observed. The effectiveness of insulin in the presence of hyperthyroidism, the effect of thyroidectomy and other details, especially those bearing on treatment, have been considered.

4 Plummer, H. S. *Functions of the Normal and Abnormal Thyroid Gland*, Oxford Medicine, New York, Oxford University Press, 1922, vol. 3, pp. 839-870.

5 Boothby, W. M., and Wilder, R. M. *Metabolism Studies in Exophthalmic Goiter Complicated by Diabetes*, *J. Clin. Investigation* **1**: 590, 1924-1925.

INCIDENCE

Fitz,⁶ in an article from this clinic on the relation of hyperthyroidism to diabetes, sketched the older literature and himself reported thirty-nine cases of diabetes complicated by thyroid disease. In some of these he dealt only with nontoxic goiter, a condition that he found had no influence on the course of diabetes. I can confirm this conclusion. In a series of fifty-two cases of nontoxic adenomatous goiter there is no evidence that the course of diabetes or the effectiveness of insulin and dietetic management was altered, either by the presence of the goiter or as a result of its subsequent surgical removal. In the balance of Fitz' cases, twenty-two in number, the goiter was toxic. He had nine cases of diabetes among 1,800 cases of exophthalmic goiter.

Table 1 indicates the frequency of occurrence of diabetes combined with states of hyperthyroidism as observed in the present series. The

TABLE 1—*Incidence of Combined Diabetes and Hyperthyroidism*^{*}

Disease	Cases	Complicating Disease	Cases	Per Cent of Total
Adenomatous goiter with hyperthyroidism	1,131	Diabetes	23	2.0
Exophthalmic goiter	2,340	Diabetes	15	0.6
Adenomatous goiter with hyperthyroidism and exophthalmic goiter, total	3,471	Diabetes	38	1.1
Diabetes	1,249	Adenomatous goiter with hyperthyroidism	23	1.8
		Exophthalmic goiter	15	1.1
		Adenomatous goiter with hyperthyroidism and exophthalmic goiter, total	38	3.0

* Mayo Clinic cases from Jan. 1, 1923, to Jan. 1, 1926.

number of combined cases is compared both to the number of cases of toxic goiter and to the number of cases of diabetes, observed during the period Jan. 1, 1923, to Jan. 1, 1926.

It appears from our clinical material that the incidence of frank diabetes as a complication of conditions of hyperthyroidism does not exceed 1.1 per cent. Its occurrence is more frequent in adenomatous goiter with hyperthyroidism (2 per cent) than in exophthalmic goiter (0.6 per cent). This is what should be expected from the fact that both diabetes and hyperthyroidism of adenomatous goiter are diseases for the most part of older people, whereas exophthalmic goiter occurs as a rule at an earlier age. In both groups the incidence of diabetes is certainly too small to justify the assumption that hyperthyroidism has much etiologic significance in diabetes. An etiologic relationship is

⁶ Fitz, Reginald. The Relation of Hyperthyroidism to Diabetes Mellitus, *Arch. Int. Med.* **27**: 305-314 (March) 1921.

occasionally suggested by the simultaneous appearance of the two diseases, but in many instances in this series the date at which diabetes appeared can be established with reasonable certainty as preceding, often by several years, the first symptoms of hyperthyroidism

THE RECOGNITION OF HYPERTHYROIDISM IN PATIENTS WITH DIABETES

The incidence of hyperthyroidism as a complication of diabetes may be somewhat greater than that shown in table 1. Seventeen cases were discarded because at the time of examination the basal metabolic rate was either normal or slightly elevated. Yet in many of these excluded cases there was good reason to believe that periods of hyperthyroidism had occurred previously. The recognition of mild grades of hyperthyroidism is often a difficult matter, and in the presence of diabetes it becomes doubly difficult owing to the fact that certain symptoms, notably bulimia, loss of weight and weakness, are common to both conditions. It should be remembered that the normal metabolism of well managed diabetic patients tends to be somewhat below the level called normal for fully nourished persons,⁷ and that the greater the degree of subnutrition the greater will be the discrepancy. Consequently, a basal metabolic rate of $+10$ or $+15$, which would be considered as within the normal range for well nourished subjects, may represent in the case of an under-nourished person with diabetes a definite stimulation from hyperthyroidism. We have come to recommend thyroidectomy when confronted with such conditions, particularly if the history suggests that periods of more intense hyperthyroidism have occurred previously.

In the presence of severe diabetic acidosis the symptoms of grave hyperthyroidism may be so masked as easily to escape detection. The following record of a case is illustrative.

REPORT OF CASE

CASE 1 (case 9, table 2) —A woman, aged 40, was admitted to the hospital, Oct 21, 1924, in deep diabetic coma with carbon dioxide combining power 11 per cent by volume and blood sugar 0.4 per cent. Thyroidectomy had been performed in 1907 for exophthalmic goiter, but the general health had been good until recently. The patient had had two children in the interval and in 1921 had passed through a febrile condition thought to be encephalitis. Symptoms suggesting diabetes had developed abruptly in August, 1924. During the year prior to this the body weight had increased 50 pounds (22.7 Kg). In the next two months it declined 30 pounds (13.6 Kg).

The thyroid gland was barely palpable and no thrill or bruit was detectable. Ocular symptoms were not pronounced, however, a faint tremor, the warmth and sweatiness of the skin, and tachycardia suggested the possibility of recurrent exophthalmic goiter. Consequently compound solution of iodine was administered in addition to the more usual anticomatose measures. The basal metabolic rate determined two days later was $+38$.

⁷ Wilder, R. M., Boothby, W. M., and Beeler, Carol. Metabolism of Diabetes, *J Biol Chem* **51** 311-357 (April) 1922.

TABLE 2—*Exophthalmic Goiter and Diabetes**

Case	Age, Sex	Disease	Duration, Months	Date	Height, Inches		Weight, Pounds		Urine Sugar for 24 Hours, Gm	Compound Solution Units of Iodine of Glucose for 24 Insulin lent of Diet, Minims Hours Gm		Date	Basal Metabolic Rate	Remarks
					Inches	Normal	Observed	Observed		Blood Sugar, Cent	Hours			
1	45 ♀	Hyperthyroidism Diabetes	3 1	6/15/23	61	160	129	24	1	0.154	20	6/15/23	+56	Ligation
				6/25/23						0.105	20	6/25/23	+20	Thyroidectomy
2	69 ♀			7/ 9/23				8				7/ 7/23		
				1/16/24			133	0		0.100	0	7/ 9/23	+13	
				4/ 6/26	61		140	0				1/16/24	+5	
				9/27/23			114	26		0.317	20	1/28/24	+72	Plasma carbon dioxide combining power, 10 per cent by volume
3	10 ♀	Recurrent hyperthyroidism Diabetes	8 2	10/29/23				92		0.276	0	10/29/23	+21	Thyroidectomy
				11/20/23				+		0.183	28	11/20/23	+27	Doing well
				12/11/23				35			0	12/11/23		
				11/ 1/24	62	133	104	±			0	11/ 1/24	+59	Thyroidectomy
4	20 ♂	Hyperthyroidism Diabetes	6 3	4/ 8/26				64		0.285	30	5/ 5/23	+14	
				12/12/24				47		0.143	30	12/12/24	-27	
				1/ 5/25				11				1/ 5/25		
				2/ 9/25				0		0.173	60	2/ 9/25		Thyroidectomy
5	43 ♀	Hyperthyroidism Diabetes	6 1	3/31/25				0		0.111	0	3/31/25	+43	
				4/ 8/26				0			0	4/ 8/26	-2	
				8/ 7/24	75	196	116	57		0.192	0	8/ 9/24	+4	
				8/14/24			145	35		0.225	90	8/19/24		Thyroidectomy
6	20 ♂	Hyperthyroidism Diabetes	8 3	8/19/24				Trace		0.100	30	9/12/24		
				9/12/24				5			30	9/13/24	-4	
				9/14/24				0			20	9/28/24	-5	
				9/26/24	61	152	130	11		0.157	0	6/11/25	+50	Chart 1
7	43 ♀	Hyperthyroidism Diabetes	6 1	6/11/25				0		0.210	0	1/ 5/25	+25	
				1/ 7/25				51		0.182	30	1/24/25	+5	
				1/23/25				9			40	1/26/25	+5	
				1/26/25				37		0.133	20	2/11/25	+38	
8	20 ♂	Hyperthyroidism Diabetes	8 3	2/11/25				0		0.113	0	12/10/25	0	
				12/ 9/25				0			0	2/ 5/24		Thyroidectomy
				4/ 6/28	69	160	129	49		0.375	15	2/15/24		Left without dismissal, untrained in dietetics
				2/ 3/24			114	0		0.110	15	2/22/24		Reported dead from diabetes
9				2/11/24				0			0	3/ 5/24		
				3/ 5/24				0			10	9/15/24		

7	63	♀	Diabetes Hyperthyroidism	4+ 2	9/ 5/25 9/14/25 10/ 8/25 10/14/25 10/22/25 4/ 9/26 7/23/25	62	180	125	+	0 350	0	Not re- stricted	9/ 4/25 9/16/25 10/ 8/25 10/12/25 10/13/25 4/ 9/26 7/18/25 7/23/25 8/ 1/25 8/ 7/25	+12 +49 +36 +39
8	44	♀	Diabetes Hyperthyroidism	? 12	8/ 2/25 8/ 9/25 8/15/25 8/18/25 4/ 6/26 10/21/24	64		217	+	0 312	0	Not re- stricted	4/ 9/26 7/18/25 7/23/25 8/ 1/25 8/ 7/25	+15 +28 +26
9	10	♀	Recurrent hyperthy roidism Diabetes	3 2	10/21/24 10/23/24 11/12/24 3/19/25	63	188	230 140	0 11	0 100	0	100	4/ 6/23 11/ 5/07 10/21/24	Not following diet Thyroidectomy Plasma carbon dioxide com bining power, 11 per cent by volume No acidosis
					10/23/24 11/12/24 3/19/25				24 0 38+	0 255	10 20 60	100 100 80	10/23/24 11/12/24 3/19/25	+38 +12
					3/25/25 3/31/25 4/14/25				27 0 15	0 241 0 241	30 45 0	100 140 140	3/25/25 3/31/25 4/14/25	+47 +20 +18
					5/12/25 1/ 2/26				0 +	0 358	40 90	140 100	5/12/25 1/ 2/26	+12
					1/11/26 1/13/26 3/18/26 7/ 9/25				14 21 0 54	0 261 0 200 0 154	60 30 30	140 100 140	1/ 5/26 1/12/26 3/18/26 7/ 2/25 7/10/25 7/16/25 7/30/25 8/ 1/25	+15 -16 +61 +27 +12
10	57	♀	Diabetes Hyperthyroidism	2+ 2	7/16/25 7/31/25 8/ 1/25 8/10/25 4/16/26	61	157	112	Trace 71 24 0 0	0 154 0 110	30 80 80 30	180 40 50 140	7/16/25 7/30/25 8/ 1/25 4/16/26	Thyroidectomy Acetonuria Diet restricted

* The records of the cases in tables 3 and 4 have been sharply abbreviated. The duration of hyperthyroidism is judged from the time of appearance of tachycardia, heat intolerance and nervousness, that of diabetes from the time of appearance of polyuria, polydipsia and glycosuria. The term "glucose equivalent" originated with Woodyatt. Its use implies the assumption that 100 per cent of the carbohydrates, 58 per cent of the proteins and 10 per cent of the fats of the diet pass through the stage of glucose during the processes of assimilation. In none of the diets did the proteins exceed 70 Gm. All blood sugar determinations were made with the Folin Wu technic on venous blood drawn in the morning before the patient had had breakfast. The insulin used was supplied by the Eli Lilly Company, and the units of insulin referred to are the clinical units standard in the United States and Canada.

† In this and table 4 ♂ indicates male, ♀ female

This patient was readmitted, March 19, 1925, again with severe acidosis, the carbon dioxide combining power of the plasma being 10 per cent by volume. She had followed instructions regarding diet and insulin fully, but on her own initiative had discontinued the taking of iodine a few days prior to this attack of acidosis. There was no history of any infection or other cause for her acidosis. In treatment, iodine was again resorted to. This time it was painted on the skin in the form of a tincture as compound solution of iodine was not retained when given by mouth or by enema because of persistent vomiting and the irritability of the rectum. After twenty-four hours, vomiting ceased and compound solution of iodine was administered by mouth. The basal metabolic rate was not determined until March 25. It was then $+47$.

In order to observe the effect of discontinuing iodine none was given after March 31, by which time the basal metabolic rate had decreased to $+20$. The diet was held constant at 2,100 calories and a glucose equivalent⁸ of 140 Gm. The insulin dosage was 90 units, and on this regimen the urine was free from sugar and acetone. The basal metabolic rate climbed gradually and reached $+48$, April 14, simultaneously sugar reappeared in the urine and increased in amount from day to day. The condition of the patient and the nervousness, tremor and tachycardia became distinctly worse. Acetone appeared and the carbon dioxide combining power of the plasma fell again to 30 per cent by volume. The use of compound solution of iodine was therefore resumed. By May 12 the basal metabolic rate was lower and with the same diet the insulin requirement had fallen to 40 units.

Jan 2, 1926, this patient was again admitted in a state of serious acidosis. Again she had been careless about iodine and discontinuing it had been followed by epigastric pain, vomiting and hyperpnea. The first basal metabolic rate was obtained January 5, it was then $+45$. Thyroidectomy was performed January 12. The weight of the tissue removed was 22 Gm. It showed hypertrophic parenchyma with areas of thyroiditis. The subsequent course was uneventful. At the last examination, April 18, 1926, the basal metabolic rate was -16 , the diet had a glucose equivalent of 140 Gm and the insulin requirement was 40 units.

This case illustrates a number of topics that will receive consideration. It is cited here particularly to emphasize how readily exophthalmic goiter may escape detection when it is complicated by the alarming symptoms of diabetic acidosis. In cases 2 and 4 (table 2) the patient was likewise in a serious state of diabetic acidosis when first seen. In neither of them was hyperthyroidism very evident, yet both patients improved rapidly after compound solution of iodine was given and might well have died had it been withheld. In the fatal case (case 12, table 2), also included in a recent report of necropsy findings in cases of diabetes,⁹ the patient was admitted in diabetic coma, exophthalmic goiter was not suspected until the pathologist found hypertrophic parenchymatous tissue in the thyroid. The possibility of hyperthyroidism should therefore be borne in mind in every case of diabetic acidosis and if suggestive symptoms, particularly tremor and marked tachycardia, are present, Lugol's solution should be given.

8 The glucose equivalent of a diet is calculated according to R. T. Woodyatt's suggestion (Objects and Method of Diet Adjustment in Diabetes, *Arch. Int. Med.* 28: 125-141 [Aug.] 1921), by the formula $G = C + 0.58P + 0.1F$, in which G is glucose equivalent, C carbohydrate, P protein, and F fat.

9 Wilder, R. M. Necropsy Findings in Diabetes, *South. M. J.* 19: 241-248, 1926.

Holst,¹⁰ from recent experience, advises examination for hyperthyroidism in all cases of diabetes. The urgent necessity for this and for thorough control of hyperthyroidism in cases of diabetes is illustrated by case 15 (table 2). This patient was an intelligent woman, a visiting nurse, well trained in the management of diabetes and very conscientious. Yet she died at her home in coma without having altered her regimen and without having acquired any infection or other cause than hyperthyroidism for this sudden exacerbation of her diabetes. She had had exophthalmic goiter and the gland was partially resected in 1911. Recurrence of symptoms required a second operation in 1914. Diabetes, acute in onset, started in January, 1922. In March, 1922, the basal metabolic rate was $+17$. In February, 1923, it was $+15$. As she was markedly undernourished these rates were probably significant.

THE EFFECT OF HYPERTHYROIDISM ON DIABETES

Contrary to the view first proposed, I think, by Friederich Muller,¹¹ there is little justification for the assumption that hyperthyroidism can initiate diabetes in an otherwise unpredisposed person. The small incidence of the combined diseases argues too strongly against it. Nor are there adequate grounds for the belief of Holst,¹² Falta¹³ and others that a special type of diabetes may be provoked by hyperthyroidism. On the other hand, there is no doubting the evidence that frank diabetes once existent is seriously aggravated by hyperthyroidism, or that a mild and possibly inconspicuous or latent spark of diabetes may be fanned into flame by hyperthyroidism.

Thyroid extract fed to normal persons will occasionally, but by no means always, provoke an alimentary type of glycosuria similar to that observed in some patients with hyperthyroidism. Such glycosuria so seldom develops into frank diabetes that when it does, as in the cases cited by Friederich Muller, it is probable that true diabetes preexisted. On the other hand, when thyroid is given to patients with diabetes, a marked intensification of glycosuria occurs and persists some time after the drug is discontinued. Grawitz¹⁴ reported such an experiment in 1897. In table 3 are the abbreviated laboratory data obtained in a case of mild diabetes in which desiccated thyroid was fed. The disease in

10 Holst, Johan. Glycosuria and Diabetes in Exophthalmic Goiter. *Acta med Scandinav* **55** 302 (June) 1921.

11 Muller, F. Discussion of paper by Kraus, F. *Verhandl d Cong f inn Med* **23** 100, 1906.

12 Holst, Johan. Kohlenhydratstoffwechselanomalien und Pankreasveränderungen bei Morbus Basedowii, Schweiz med Wchnschr **53** 725-729 (Aug 2) 1923.

13 Falta, W. *Endocrine Diseases*, ed 3, Philadelphia, P Blakiston's Son & Co., 1923, p 88.

14 Grawitz, E. Morbus Basedowii compliziert mit Diabetes Mellitus nebst Bemerkungen über Iodthyriwirkung, *Fortschr de Med* **15** 849-853, 1897.

this case was under good control by diet without the use of insulin. The diet was held constant and for a period of nine days, beginning April 25, a total of 42 grains (3 Gm.) of desiccated thyroid was administered. This produced an elevation of the basal metabolic rate from an average level of -7 to a maximal of $+20$, and coincidentally sugar appeared in the urine in amounts exceeding that which could possibly be accounted for by the accompanying accelerated catabolism of protein. When the drug was discontinued glycosuria persisted to such an extent that a restricted dietary and insulin were necessary to control it. Later, after the basal metabolism had again fallen to normal, the previous good tolerance returned.

TABLE 3—*Effect of Thyroid on Tolerance in a Case of Mild Diabetes**

Date, 1925	Desiccated Thyroid, Grains	Basal Metabolic Rate	Blood Sugar, per Cent	Urine	
				Sugar, Gm.	Nitrogen, Gm.†
4/22			0.100	0	8
4/23		-7	0.112	0	7
4/24		-7	0.102	0	10
4/25	3	-12	0.118	0	7
4/26	9				
4/27	9	-8	0.143	5	14
4/28	3	$+15$	0.156	12	7
4/29	3	$+16$	0.171	15	10
4/30	3	$+8$	0.144		
5/1	5	$+14$	0.156	20	9
5/2	6	$+15$	0.185	37	20
5/3	2	$+19$			
5/4		$+20$	0.153	24	12
5/5			0.154	42	18
5/6		$+19$	0.154	24	14
5/17				0	7
5/18				0	8
5/19		-3	0.118	0	7

* The diet consisted of carbohydrates, 98 Gm., proteins, 48 Gm., and fats, 242 Gm., glucose equivalent, 150 Gm.

† Twenty-four hours

A number of cases could be cited to illustrate the fact that preexisting diabetes is markedly intensified by the occurrence of hyperthyroidism. The date of onset in hyperthyroidism is often difficult to determine. The same is true in diabetes. In the following case, however, it is reasonably certain that diabetes had existed for at least two years while hyperthyroidism was not older than six months.

CASE 2 (case 4, table 4)—A woman, aged 59, developed marked polyuria and polydipsia in February, 1922. Sugar was found in the urine, but this was readily controlled by a diet until, in August, 1924, symptoms suggestive of hyperthyroidism were noted for the first time. These were nervousness, intolerance to heat, increased perspiration and tachycardia. Thereafter, dieting proved ineffectual, and at the time of admission to the hospital, Feb. 16, 1924, the urine contained an abundance of sugar and the blood 0.252 Gm. of sugar for each 100 cc. On a diet with a glucose equivalent of 140 Gm. an average of 50 Gm. of sugar appeared in the urine daily. The basal metabolic rates ranged from $+52$ to $+66$. Later, glycosuria was controlled with insulin, 40 units daily, and, March 5, thyroidectomy was performed. Thyroid tissue weighing 372 Gm. was removed, this showed multiple adenomas. The convalescence was uneventful, the basal metabolic rate fell, and by March 26 the same diet, previously requiring 40 units of insulin, could be taken without insulin.

TABLE 4—*Adenomatous Goiter with Hyperthyroidism and Diabetes*

Case	Age, Sex	Disease	Duration, Months	Date	Height, Inches		Weight, Pounds		Urine Sugar, for 24 Hours, Gm	Blood Sugar, per Cent	Compound Solution of Iodine, for 24 Hours, Minims		Glucose Equivalent of 24 Diet, Gm	Date	Basal Metabolic Rate	Remarks
					Normal	Observed	Normal	Observed			Hours	Minims				
1	66 ♀	Diabetes Hyperthyroidism	6 3	9/21/25 9/29/25 10/ 8/25 10/29/25	62	170	126	Trace	Trace	0.211	0	0	0	9/22/25 9/29/25 10/ 7/25	+43 +37	Thyroidectomy
2	58 ♀	Diabetes Recurrent hyperthyroidism	36	4/ 7/26 6/12/25 6/15/25 6/20/25 7/ 3/25 4/ 8/26 4/ 9/23 4/13/23 4/17/23 4/28/23	61	150	146 98	Trace 11 14 12 0 0	Trace	0.230 0.176 0.126	0 0 0	0 0 0	0 0 0 0 0	05 6/10/25 6/17/25	+29	Thyroidectomy Thyroidectomy Thyroidectomy
3	54 ♀	Hyperthyroidism Diabetes	12 6	4/ 9/23 4/13/23 4/17/23 4/28/23 2/18/24 3/ 7/24 3/26/24 7/17/24 10/ 7/24	62	170	136	4 15 67 0 Trace	Trace	0.182	10 10 10 0	25 25 10 0	80 145 75 100 115 140 100 150	4/ 9/23 1/13/23 4/16/23 4/28/23 2/18/24 3/ 5/24 3/26/24 7/17/24 10/ 7/24	+51 +41 +15 +66 +9	Thyroidectomy Thyroidectomy Thyroidectomy Thyroidectomy Well Died, acute cholecystitis?
4	50 ♀	Diabetes Hyperthyroidism	24 6	2/18/24 3/ 7/24 3/26/24 7/17/24 10/ 7/24	64	206	124	64 20 0	Trace	0.252 0.265	0 0	0 0	0 0	12/ 3/24 12/ 6/24 12/16/24	+42 +21	Thyroidectomy
5	51 ♀	Hyperthyroidism Diabetes	36 30	12/ 6/24 12/15/24 12/18/24 1/30/25 1/ 2/26 7/ 1/24 7/ 9/24 7/15/24 7/29/24	61	160	150	11 0 40 0 0	11 0 0 0	0.227 0.200 0.286 0.133	0 0 30 20	0 0 30 0	0 0 35 70 50 70	7/ 2/24 12/ 3/24 12/ 6/24 12/16/24	+36	Thyroidectomy
6	53 ♀	Diabetes Hyperthyroidism	34 6	8/18/25 7/ 1/24 7/ 9/24 7/15/24 7/29/24	63	170	101	84 0 55 0	84 0 0	0.227 0.200 0.250	0 0 0	0 0 0	0 0 0	7/ 2/24 12/ 3/24 12/ 6/24 12/16/24	+12	Thyroidectomy
7	49 ♀	Hyperthyroidism Diabetes	12 4	7/ 6/25 7/19/25 8/ 4/25 4/ 7/26 1/10/24 1/22/24 1/29/24 2/15/24 4/15/23	63	245	180	14 10 0 +	14 10 0 +	0.206 0.117	20 30 0	30 40 0	150 150 140 135	7/ 6/25 7/17/25 8/ 3/25 1/15/24 1/22/24 1/28/24	+30 +8	Thyroidectomy Thyroidectomy
8	56 ♀	Hyperthyroidism Diabetes	12 13	1/10/24 1/22/24 1/29/24 2/15/24 4/15/23	59	145	123	115 Trace 50 0	Trace	0.270 0.157	0 0 0	0 20 40 0	0 60 100 120	1/15/24 1/22/24 1/28/24	+37 +23	Thyroidectomy

9	44 ♀	Diabetes Hyperthyroidism	60 48	12/11/24 12/26/24 1/ 5/25 4/ 7/26	64	153	110	Trace 22 0	0 176 45 0	0 0 0	0 0 0	100 100 100	12/13/24 12/24/24 1/ 5/25	+18 -12	Thyroidectomy
10	62 ♂	Diabetes Hyperthyroidism	240 6	10/27/24 11/ 5/24 11/ 7/24 12/ 4/24 1/11/26 4/ 8/26	67	210	159	61 5 97 0 0 0	0 200 30 30 0 0 0	0 65 80 0 0 0	0 140 140 100 100 100	10/27/24 11/ 4/24 11/ 6/24	+40 +30	Thyroidectomy Subsequent admission	
11	45 ♂	Diabetes Hyperthyroidism	108 18	8/21/25 8/25/25 9/14/25 4/ 6/26	68	210	163	Trace 25 0	0 171 0 0 095	0 0 0	0 90 100 140	8/21/25 8/24/25	+30	Thyroidectomy	
12	63 ♀	Diabetes Hyperthyroidism	72 ?	6/30/25 9/13/25 9/24/25 4/ 6/26	66	220	180	Trace Trace 0	0 155 30 0 154	0 30 0	0 140 100 140	6/29/25 9/11/25	+32	Thyroidectomy	
13	56 ♂	Diabetes Hyperthyroidism	120 4	10/28/24 11/15/24 11/26/24	68	180	140	13 4 0	0 182 0 213 0 143	0 40 30	0 100 150	10/28/24 11/14/24 11/26/24 6/ 9/25	+30	Thyroidectomy Heart weak, coronary sclerosis Sudden death due to heart	
14	46 ♀	Diabetes Hyperthyroidism	60 48	10/12/24 11/ 3/24 11/ 5/24 11/14/24 10/26/25	56	180	164	50 Trace + + +	0 250 0 194 0 235 0 110	0 30 30 0	0 30 100 140	10/21/24 10/28/24 11/ 4/24 11/11/24	+20 +11 + 7	Thyroidectomy	
15	62	Hyperthyroidism Diabetes	12 ? 8	2/29/24 5/23/24 4/ 7/26 4/25/25 5/10/25	60	165	121	0 0 0 Trace 10	0 120 0 158 0 162 0 201	0 0 0 0	0 0 0 20	2/29/24 5/24/24 4/28/25 5/ 8/25	+23 +30	Thyroidectomy Thyroidectomy	
16	62 ♀	Hyperthyroidism Diabetes	? 9	4/25/25 5/10/25 4/ 6/26	64	225	191	Trace 10 0	0 162 0 201	0 0	0 95	4/28/25 5/ 8/25	+30	Thyroidectomy	
17	52 ♀	Diabetes Hyperthyroidism	17 12	7/18/23 8/ 1/23 8/ 7/23 4/15/26	61	170	130	Trace 44 ?	0 190 0 0	0 40 0	0 160 160	7/18/23 7/31/23	+18	Thyroidectomy	
18	65 ♂	Hyperthyroidism Diabetes	48 48	10/18/23 11/ 7/23 11/12/23 8/ 2/23	68	195	128	17 19 0	0 10 0	0 20 0	0 200 100 140	10/19/23 11/ 6/23	+16	Thyroidectomy	
19	56 ♀	Hyperthyroidism Diabetes	24 24	8/ 2/23 8/ 9/23	64	175	138	5 7	0 200 0 246	0 0	0 140	7/30/23 7/31/23 8/ 6/23 9/ 3/23	+42 +25	Thyroidectomy Amputation of breast for car cinoma Died, recurrent carcinoma	

TABLE 4—Adenomatous Goiter with Hyperthyroidism and Diabetes—Continued

Case No.	Age, Sex	Disease	Duration, Months	Date	Weight, Pounds		Urine Sugar for 24 Hours, Gm	Compound Solution of Iodine of Blood Sugar, for 24 Hours, Cent		Glucose Equivalent of Diet, Gm	Date	Basal Metabolic Rate	Remarks
					Height, Inches	Normal	Observed						
20	15	Hyperthyroidism Diabetes	14	8/21/23	64	148	128	14	0.197	0	130	+23	Thyroidectomy
				8/27/23			45		0	20	130	+23	
				8/30/23			70	0.250	0	20	130		
				9/8/23			0	0	0	20	130	+16	
				9/11/23			0	0	0	0	130		
21*	65	Diabetes Recent hyperthyroidism	36?	4/6/26			145	Trace	0	0	80	+18	Thyroidectomy
				1/13/23	69	180	152	11	0.240	0	Not restricted		
				4/27/23			45	0.263	0	Restricted	4/23/23		
				5/21/23			5			Restricted	5/22/23		Suprapubic cystostomy for carcinoma
				5/23/23			29	0.325	60	100			
											5/30/23		Death from acidosis, pneumonia and uremia
Cases Without Operation													
					Weight, Pounds		Height, Inches						
					Normal	Observed							
22	72	Hyperthyroidism Diabetes	31	61	?	95							Hospital observation from Oct 17 to Nov 11, 1923. A small adenomatous thyroid, marked arteriosclerosis and dilatation of the heart were noted, on admission, despite a previously restricted diet, the urine contained sugar and the blood sugar was high, 0.305 per cent, although the diet was further restricted to a glucose equivalent of 40 Gm, the glycosuria and hyperglycemia persisted and could only be controlled by relatively large doses of insulin. The basal metabolic rates were +20 and +11. A second hospital observation was made Dec 20, 1923, at which time the patient was bedridden because of increased weakness and cardiac decompensation, basal metabolic rate +20, compound solution of iodine was given and a later basal metabolic rate was +9, the patient steadily declined, was discharged and died at her home Feb 19, 1924, necropsy was not performed.
			31										
23	63	Diabetes Hyperthyroidism	180	61	137	125							Hospital observation from July 10 to Aug 16, 1924. Basal metabolic rates, +25, +22 and +21, 30 units of insulin required with diet with glucose equivalent of 90 Gm, the fasting blood sugar, August 7, was 0.191 per cent, thyroidectomy not advised because of evidence of complicating angina pectoris, report, April 6, 1926, was weight, 136 pounds, urine sugar, 0, 10 units of insulin daily and diet restricted
			?										

* After the prostatic operation this patient developed an acute exacerbation of his mild diabetes, possibly the result of infection in the wound from thyroidectomy, old abscess seen at necropsy

In this patient a mild diabetes was made fairly severe by the development of hyperthyroidism, and resumed its mild state after the control of the latter by thyroidectomy

Hyperthyroidism, as is well known, is wont to show alternating periods of exacerbation and remission. This is true both in that accompanying adenomatous goiter and in exophthalmic goiter, although it is much more common in exophthalmic goiter. Exacerbations may occur spontaneously and these at times assume the intense form of the hyperthyroid crisis. When diabetes coexists, any exacerbation is associated with intensified glycosuria and this may be so extreme that not enough sugar is burned to prevent ketosis. Under such circumstances acetone formation goes on apace, and serious acidosis and coma may result. In case 1 (case 9, table 2) already cited in detail, there is good reason to believe that the three attacks of diabetic acidosis, the first two actual diabetic coma, were precipitated in this manner. The same is probably true of cases 2 and 4 of table 2.

It is furthermore a frequent occurrence to have an exacerbation of hyperthyroidism within from six to twenty-four hours after thyroidectomy, and in patients with complicating diabetes one almost always sees an exacerbation of the diabetic condition on the day following operation. Large doses of insulin, from 80 to 100 units daily, may be necessary for its control (tables 3 and 4).

THE INFLUENCE OF IODINE ON THE INTENSITY OF DIABETES

In cases of diabetes uncomplicated by hyperthyroidism iodine is without observable effect. At the Mayo Clinic, I have administered it periodically to a large group of patients with diabetes and have been unable to detect any change in tolerance attributable to it. In cases of diabetes with adenomatous goiter and hyperthyroidism it has likewise been ineffectual except in a few instances in which the diagnosis of coexisting exophthalmic goiter could not be excluded. In cases of diabetes complicated by frank exophthalmic goiter the influence of iodine on the intensity of the diabetic process is as striking as its effect on the exophthalmic goiter syndrome. Labbé¹⁵ noted this in 1920. The urine sugar in a case of this kind, which he treated with iodine, dropped from 208 to 71 Gm., while coincidentally palpitation and tachycardia were favorably affected. The data recorded in table 2 show how uniformly the administration of compound solution of iodine improves the tolerance in cases of diabetes complicated with exophthalmic goiter. The phenomenon is well illustrated by the following case (chart 1).

¹⁵ Labbé, Marcel. *Diabète et goitre exophtalmique*, *Ann. de med.* **7** 95-103, 1920.

CASE 3 (case 5, table 2)—A woman, aged 43, was admitted Jan 1, 1925. She had had a nervous breakdown in the spring and had been weak all summer. Definitely recognizable diabetic symptoms, polyuria and polydipsia had been noted in November. Sugar had been found in the urine and a restricted diet had been prescribed. The urine was said to have been sugar free three months before. There was a striking familial record of diabetes, four instances on the maternal side and one on the paternal side.

At the time of admission, the blood sugar was 0.271 Gm for each 100 cc. The urine contained very little sugar at first, but with a more liberal diet (1,800 calories, glucose equivalent, 120 Gm) glycosuria increased, and from January 4 to 10 a very constant excretion of about 55 Gm a day occurred. January 9, a daily administration of 30 minims of compound solution of iodine was started. This was followed by a noticeable diminution in glycosuria which had fallen by January 20 to 6 Gm. Insulin was then given in a dosage of 10 units twice daily and, January 26, thyroidectomy was performed. The pathologist reported hypertrophic parenchymatous thyroid tissue weighing 15 Gm. Large doses of insulin were required for three days following the operation, but subsequently they could be discontinued without recurrence of glycosuria.

This patient was examined again, Dec 3, 1925. She had adhered to her diet and found no sugar in the urine during the interval. Basal metabolic rates were +11 and +6. The carbohydrate in the diet was increased so that the glucose equivalent would be 250 Gm and still the urine remained sugar free. A test meal of 100 Gm of glucose was given and the urine contained no sugar, although the blood sugar curve shown in figure 2 is obviously not normal.

THE EFFECTIVENESS OF INSULIN WHEN DIABETES IS COMPLICATED BY HYPERTHYROIDISM

It is well known that when diabetes is complicated by infections the insulin requirement may be materially increased. Similarly when hyperthyroidism is the complication, it is always necessary to use more insulin than would be needed in an uncomplicated case. This is apparent from a perusal of the data given in tables 2 and 4. It is also evident in the course of case 1 (case 9, table 2). March 31, 1925, twelve days after the second admission of this patient, the urine was held sugar free by 90 units of insulin. At this time the diet contained 2,100 calories and had a glucose equivalent of 140 Gm. Discontinuing the administration of iodine was followed by a gradual upward swing of the basal metabolic rate and the excretion of from 10 to 15 Gm of sugar despite the high insulin dosage. The resumption of the daily dose of iodine was followed in time by a decline of the basal metabolic rate and a reduction of the insulin requirement to 40 units.

THE VALUE OF THYROIDECTOMY IN PATIENTS WITH COMBINED DIABETES AND HYPERTHYROIDISM

While the time elapsed since this group of patients has been under observation is short, the immediate results have been so very satisfactory and the present condition of a large majority of these patients is so encouraging that there can be little question of the value of thyroidectomy for them. When Fitz⁶ wrote on this subject he was not encouraged

with the results of operation. Of twelve of his patients with toxic goiter two died immediately after the operation. Several others succumbed to diabetes within the next few years. However, in four of his cases the intensity of diabetic manifestations was very strikingly lessened and apparently life was prolonged. That was in 1920. Since that date the methods of treating diabetes have improved tremendously, due mainly to the great discovery of Banting and McLeod, also the risk of exophthalmic goiter has been distinctly lessened by Plummer's ¹⁶ demonstration of the value of iodine in its treatment. The patient with diabetes no longer presents the serious surgical risk that he did. Consequently, he can and should receive the same surgical benefits from thyroidectomy as are available to his less handicapped fellow, provided, naturally, that all the special precautions necessary in his case are taken.

Of the thirty-three patients with hyperthyroidism in this series for whom thyroidectomy was performed, none died as a result of the operation. An improvement in tolerance has occurred within a week or ten days after thyroidectomy in almost every case. In many this improvement has not made it possible or advisable to discontinue the use of insulin. In others it has been so pronounced as to constitute an arrest of the diabetic state. I have quoted the record of one of these in some detail (case 3, chart 1). Thyroidectomy was performed, Jan 26, 1925, and this was followed in a few days by such a sharp improvement in tolerance that insulin could be discontinued. At a later examination, Dec 3, 1925, a very rich carbohydrate allowance could be taken without glycosuria being provoked, and a test meal of a 100 Gm of glucose caused no glycosuria.

There are a number of case reports in the literature of recovery of normal tolerance after thyroidectomy ¹⁷. In none of them, so far as I have been able to find, was the blood sugar determined after glucose test meals. Without such examinations it is scarcely legitimate to claim, as some have done, that an actual cure has followed the removal of the thyroid. Holst ¹² reports observations on several instances of persistent glycosuria in two of which glucose test meals after recovery from thyroidectomy failed to cause glycosuria. It is highly probable that these most favorable results merely represent the arrest of a latent diabetic condition. In case 3 there must have been a latent diabetes before hyperthyroidism developed. The familial history speaks strongly for it. This

¹⁶ Plummer, H. S., and Boothby, W. M. The Value of Iodine in Exophthalmic Goiter, *J. Iowa State M. Soc.* **14** 66-73 (Feb.) 1924.

¹⁷ O'Day, J. C. Diabetes in Association with Toxic Goiter, *New York M. J.* **111** 815-816 (May 8) 1920. Holst (footnotes 10 and 12). Rohdenburg, G. L. Thyroid Diabetes, *Endocrinology* **4** 63-70 (Jan-March) 1920. Buchanan, J. A. A Case of Exophthalmic Goiter and Diabetes Mellitus, *M. J. & Record* **119** 11-13 (Jan 2) 1924. Rohdenburg, G. L. A Case of Spontaneous Disappearance of Diabetes, *Endocrinology* **6** 519-522 (July) 1922.

condition was fanned into life by hyperthyroidism, and when the latter was controlled it subsided again to its original state of latency. Blood sugar determinations made after the glucose test meal (chart 2) were not quite normal, the delayed return to the fasting blood sugar level strongly suggesting the continued presence of diabetes.

MYXEDEMA AND DIABETES

Some of the reputed recoveries of normal tolerance after thyroidectomy may be due to the development of myxedema. In a case reported by Holst¹² diabetes was manifested six months after thyroidectomy for exophthalmic goiter, during a recurrence. Two and one-half years later myxedema appeared spontaneously and then a test meal of 100 Gm of glucose provoked no alimentary glycosuria. Several instances of myxedema occurring in the course of diabetes and resulting, as in Holst's case, in great amelioration of the tolerance are to be found in the literature. A most interesting example of this was recently seen here.

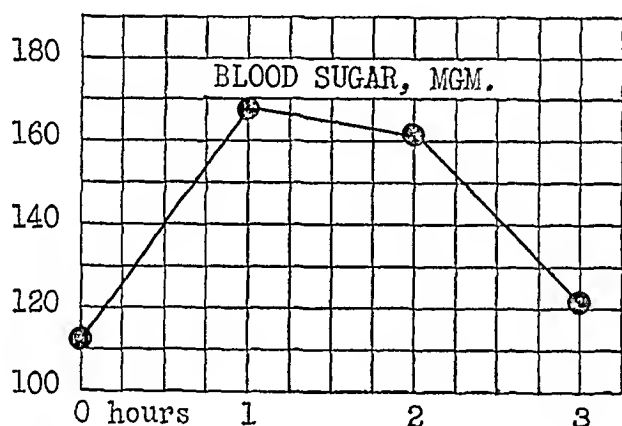


Fig 2 (case 3)—Blood sugar curve after giving of test meal of 100 Gm of glucose, the urine contained no sugar

CASE 4—A male child, aged 7, had been a full term infant with normal health and normal growth up to the age of 15 months. He then manifested polydipsia and polyuria, and sugar was found in the urine. He was placed on a strict diet which, after six months, could be somewhat relaxed without causing a return of glycosuria. Delayed growth and increasing coarseness of the hair led to the diagnosis of hypothyroidism, when he was aged 3. Thyroid treatment was begun but was discontinued because of the return of intense glycosuria and the occurrence of acidosis. During the period of thyroid treatment growth had been resumed. After its discontinuance growth again stopped and the tolerance improved so much that the child "could eat anything without excreting sugar."

On examination at the clinic this patient presented a fully developed picture of juvenile myxedema, the face dull and expressionless, the skin dry and thick, the hair coarse and scanty. Mentality and physical development were much retarded, the height was 38.5 inches, the weight 34 pounds (15.4 Kg). The basal metabolic rate was -45 . The urine was sugar free, the blood sugar, 0.12 per cent.

There was some difference of opinion among the examining physicians as to whether the child could have had diabetes. My prediction was that when the metabolic rate was raised to normal, diabetes would be evident and insulin would be needed in order to make possible the feeding of a satisfactory diet. Thyroid was

administered in small doses and the metabolism raised very gradually. At the same time the diet was rigidly restricted in carbohydrate and protein. August 2, the basal metabolic rate reached — 10 and sugar appeared in the urine. Later under the reestablished metabolic rates sugar continued to be excreted in amounts as high as 20 Gm a day, and the fasting blood sugar level reached 0.145 per cent. At the last report, Dec 29, 1925, the child was gaining in weight and strength but showing sugar despite a rigid diet (glucose equivalent 76 Gm) and 10 units of insulin daily.

This case lends considerable support to the theory that with lower metabolic rates the tissue cells can utilize a given amount of glucose with less insulin than they require when the metabolism is pitched at a higher rate. The case further indicates that we are not justified in concluding that diabetes has been cured by thyroidectomy unless we can show that the basal metabolic rate has not been reduced below normal in consequence of the operation or of a thyroiditis following operation.

TREATMENT

Thyroidectomy will be clearly indicated in the large majority of cases of combined diabetes and toxic goiter. Nevertheless, the operation should not be undertaken unless the surgeon is familiar with the measures necessary to protect his patient from the effects of the operation. The period of exacerbated toxicity which so frequently follows on the heels of thyroidectomy is extremely dangerous to a patient with diabetes.

In a case of diabetes even greater care should be taken in preparation for thyroidectomy than is necessary with other operations in the presence of diabetes. Normal water balance should be restored, glycosuria and particularly any acidosis should be controlled, and an effort should be made to bring up the general nutrition and to replenish as far as possible the depleted stores of glycogen.¹⁸ The diet of these patients must be richer than is necessary or advisable for other patients with diabetes. The food calories should equal at least twice the normal basal caloric requirement and the allowance of carbohydrate should be fairly liberal (100 Gm or more). There seems to be no advantage in giving more than 50 or 60 Gm of protein.

In order to check glycosuria while the liberal diet is being fed, insulin will be required. It is often necessary to inject insulin at six hour intervals. A close watch must be kept to avoid acidosis on the one hand and hypoglycemia on the other. These patients are peculiarly sensitive to the latter, due probably to the fact that the liver in cases of hyperthyroidism may be poor in glycogen.¹⁹

18 Holman, E F. Hypoglycemia in Exophthalmic Goiter, *Bull Johns Hopkins Hosp* **34** 69-70 (Feb) 1923.

19 Richardson, H B, Levine, S Z, and DuBois, E F. Clinical Calorimetry. xli. The Storage of Glycogen in Exophthalmic Goiter, *J Biol Chem* **67** 737-751, 1926. Sanger and Hun (footnote 3). Holman (footnote 18).

A diagnostic criterion of importance in the coma from hypoglycemia is the blood pressure. This is usually sharply elevated during insulin reactions. I have seen the systolic pressure as high as 220 mm of mercury during hypoglycemic coma in a patient whose systolic pressure was ordinarily 120. It falls again within half an hour after the blood sugar is restored to normal. So far as I know, this hyperpiesis from insulin has not been reported heretofore. It is due probably to the liberation of epinephrine, a spontaneous attempt at the restoration of a normal blood sugar²⁰

Because of the peculiar sensitiveness of these patients to hypoglycemia it is better not to attempt the complete control of glycosuria until some days after operation. The persistence of traces of sugar in the urine (from 5 to 10 Gm in a twenty-four hour specimen) seems to have no ill effect either on the resistance of the patient or on the healing of the operative wound.

Compound solution of iodine is given in doses of from 1 to 3 cc daily; the usual dose is 10 minims (0.6 cc) three times daily. In cases of adenomatous goiter with hyperthyroidism iodine may be ineffective, but since it is not always possible to exclude exophthalmic goiter and since iodine can do no harm in any case of hyperthyroidism, during the short period while the patient is being prepared for operation, it seems best to use it as a routine when the basal metabolic rate is elevated. If the patient is in diabetic coma and unable to retain medicines given by mouth or by rectum, sufficient absorption of iodine can be secured by painting a 5 per cent tincture of it on the skin. The operation should be deferred until a maximal iodine effect has been obtained and the patient has recuperated as much as possible. This may require from two to three weeks. The criterion of operability in exophthalmic goiter has been discussed recently by Pemberton²¹. Prolonged deep general anesthesia should be avoided. After operation fluids should be given in abundance and sugar (glucose) administered by mouth, by rectum or by vein so that the patient receives 100 Gm of it daily. The diet can usually be resumed by the second or third day.

If a thyroid reaction results from the operation the doses of iodine and insulin must be increased. It is frequently necessary to give 1 cc

20 Cannon, W. B., McIver, M., and Bliss, S. W. The Effect of the Blood Sugar Level on Adrenal Secretion and Sympathetic Activity, A Preliminary Note, *Boston M. & S. J.* **189** 141-142 (July 26) 1923. Boothby, W. M., and Wilder, R. M. Preliminary Report on the Effect of Insulin on the Rate of Heat Production and Its Significance in Regard to the Calorigenic Action of Adrenalin, *M. Clin. N. Amer.* **7** 53-56 (July) 1923. Wilder, R. M., Boothby, W. M., Barborka, C. J., Kitchen, H. D., and Adams, S. F. Clinical Observations on Insulin, *J. Metab. Research* **2** 701-728, 1922.

21 Pemberton, J. D. Present Day Surgical Treatment of Diseases of the Thyroid Gland, *J. A. M. A.* **85** 1882-1886 (Dec 12) 1925.

of compound solution of iodine every six hours and to use as much as 20 units of insulin every six hours. The insulin dosage must be controlled by frequent examinations of the urine and blood, as the danger of hypoglycemia seems to be particularly great shortly after the operation.

It is important to give these patients a thorough training in dietetics and in the management of diabetes. The time of their convalescence should be used for imparting this information to them. While diabetes may occasionally be arrested by thyroidectomy and will be decreased in intensity in most cases, it will nevertheless remain after the thyroid element of the combined diseases has been removed. These patients deserve, therefore, the same consideration from the standpoint of diabetes as do others with diabetes.

While there has been no recurrence of hyperthyroidism in this group in which thyroidectomy was recently performed. It is considered advisable before dismissing these patients to caution them against the danger of postoperative recurrence so that they may be prepared to return promptly for further treatment in case thyroid symptoms should manifest themselves anew. In the presence of such recurrence an attempt is made to control the disease with iodine, but if this fails further resection is advisable.

COMMENT

Mention was made in the introductory remarks of studies of the respiratory quotient of patients with toxic goiter, and it was stated that such studies definitely rule out the supposition that the fairly common alimentary hyperglycemia of the patient with hyperthyroidism means diabetes or a true disturbance of carbohydrate metabolism. The phenomena exhibited by patients with true diabetes combined with states of hyperthyroidism or hypothyroidism appear to be definitely related to the general metabolic rate, and therefore are susceptible of explanation without recourse to speculation as to a specific interdependence of thyroid and pancreas.

Fitz suggested that the unfavorable influence of hyperthyroidism in diabetes might be due to the resulting increased rate of total metabolism rather than to any direct effect of the thyroid gland on carbohydrate metabolism. Allen²² shared this view. The idea, as expressed both by Fitz and Allen, was based on the well established observations, particularly those of Allen, that fasting, wasting diseases and other conditions that lower the basal metabolism act favorably on the tolerance of the patient with diabetes, whereas overfeeding which raises the general

²² Allen, F. M. *Studies Concerning Glycosuria and Diabetes*, Boston, Harvard University Press, 1913, pp. 842-851, *Experimental Studies in Diabetes, Internal Pancreatic Function in Relation to Body Mass and Metabolism, Influence of Thyroid upon Diabetes*, *J. Metabolic Res.* **1**: 619-665 (May) 1922.

metabolism acts unfavorably Boothby and I⁷ have pointed out that the influence of heavy protein dietaries in diabetes is much like that of hyperthyroidism in that such diets stimulate the metabolism by their high specific dynamic actions and that as the metabolic rate rises the tolerance falls Fever, as is well known, elevates the metabolic rate and simultaneously depresses sugar tolerance Pregnancy does the same to a lesser extent The action of drugs with a calorogenic influence has thus far not been studied except in the case of thyroxin and epinephrine, both of which lower tolerance

In general, it appears that all those measures or conditions which stimulate the general metabolism have a depressing action on the tolerance of the diabetic patient similar to that of hyperthyroidism, whereas sedative drugs, such as opium, and conditions which lower the general metabolism act in diabetes like hypothyroidism I am aware of only one exception to this generalization, namely, exercise As is well known, muscular work, while raising the rate of heat production enormously, does not provoke a decreased tolerance in diabetes The reverse may be the case A number of patients, those who pursue especially arduous labor, such as farming, are provided with two diets, a richer work day diet and a lighter Sunday diet If they take their work day diet on Sunday they show sugar or require more insulin, if they limit their diet on work days to their Sunday allowance without at the same time reducing their dose of insulin, they develop symptoms of hypoglycemia This unique position of exercise among factors affecting the metabolic rate is worthy of attention It suggests that there exists a fundamental difference between the heat production attending muscular contraction and that associated with the chemical processes that are stimulated by food and by calorogenic agents such as thyroxin

Three facts, that iodine increases the tolerance of diabetic patients with exophthalmic goiter (in which condition it reduces the metabolic rate), that it has no such influence on the tolerance of those diabetic patients with hyperthyroidism due to overfunctioning of adenomatous goiter (in which it does not affect the metabolic rate), and that it has no influence on uncomplicated cases of diabetes, are perhaps the most important contributions of the present study This evidence is, I think, incontrovertible and strengthens considerably the argument that the rate of the general metabolism governs the efficiency of carbohydrate utilization

The data thus far presented have shown that the requirement of insulin of patients depending on large doses of the drug is increased by hyperthyroidism To test this further thyroxin was injected in a patient with very severe diabetes who required a daily injection of 50 units of insulin for a diet with a low glucose equivalent (100 Gm) This caused

no glucose excretion until after twenty-four hours. In the second twenty-four hours the sugar output was 25 Gm, but by then the basal metabolic rate had been elevated from -10 to $+23$. Also, thyroxin and insulin have been put in solution together and left standing in vitro for seventy-two hours without loss of activity of the insulin. These facts are difficult to explain either on the assumption that the thyroid hormone depresses the pancreas or that the thyroid secretion directly neutralizes insulin. A more probable explanation, in complete harmony with the available clinical and experimental observations, is the following:

The tissue cell, with a metabolism accelerated by thyroxin, requires for a given amount of glucose an amount of insulin that is disproportionately greater than its requirement when its metabolic exchanges are performed at a more leisurely tempo. The higher the metabolic rate the greater is the demand for insulin, even though the total amount of sugar to be utilized in a given time remains constant. The lower the metabolic rate the less the amount of insulin required to do the same work in the same time.

It is possible to suggest several ways by which the apparent insufficiency of insulin in hyperthyroidism might be explained. A simple one that serves at least to correlate the observed facts may be that insulin is more rapidly destroyed when hyperthyroidism exists. The effect of an injection of insulin is short lived at best, from six to twelve hours. The evanescent character of the action of biologic catalysts in general seems to be due to the gradual destruction of such catalysts by the tissues, a destruction attributable to the action on them of catabolic processes. Therefore, it is probable that when oxidations are proceeding at a relatively rapid rate a catalyst, such as insulin, undergoes a more rapid decay, whereas its life may be longer and therefore its efficiency greater when oxidations are taking place more slowly.

Patients with no diabetes, and consequently with large supplies of insulin, reveal no lack of tolerance for carbohydrates, even when their metabolism is stimulated by extreme grades of hyperthyroidism, because their supply of insulin is more than adequate to meet the disproportionately large demands resulting from the accelerated metabolism. In diabetic patients the situation is altered by the fact that the supply of insulin has been limited and a factor of safety, otherwise enjoyed, no longer exists. Therefore, an elevation of the metabolic rate, which in normal persons may be associated with evidence of actual acceleration of carbohydrate metabolism, is attended in the diabetic organism by a paradoxical decrease in carbohydrate metabolism. A diabetic patient with hyperthyroidism is like a man of small means with a wasteful wife. By careful spending both ends might be made to meet, but the squandering of limited resources soon results in disaster.

SUMMARY

This is a study of thirty-eight cases of frank diabetes combined with states of hyperthyroidism and of one case of diabetes associated with myxedema. The association of diabetes and hyperthyroidism occurs with a frequency of about 11 per cent of all cases of hyperthyroidism. Exophthalmic goiter is less frequently complicated by diabetes (0.6 per cent of all cases) than adenomatous goiter with hyperthyroidism (2 per cent). The study is not concerned with alimentary glycosuria, which is a much more common phenomenon in cases of hyperthyroidism and does not represent, in my opinion, any actual abnormality of carbohydrate metabolism as herein defined.

The symptoms of hyperthyroidism in a patient with diabetes may be obscured by those of diabetes. This is particularly true in cases with severe acidosis or diabetic coma. It is advisable, therefore, to consider the possibility of hyperthyroidism in all cases of diabetic acidosis.

A mild and possibly inconspicuous diabetes may be fanned into flame by hyperthyroidism, and severe hyperthyroidism (crisis) will readily provoke coma in a diabetic patient.

The requirement of insulin is increased by hyperthyroidism.

Iodine, administered as compound solution in a dosage of from 20 to 60 minims daily to patients suffering from combined exophthalmic goiter and diabetes, reduces the intensity of the diabetes. This effect parallels that on the basal metabolic rate. Iodine has little or no influence on the course of diabetes associated with adenomatous goiter with hyperthyroidism, and is without effect in cases of uncomplicated diabetes.

Thyroidectomy is almost always followed by a considerable gain in tolerance in diabetes complicated by hyperthyroidism. Sometimes this is so great as to suggest an actual cure of diabetes, but the response to glucose test meals may still reveal the persistence of the diabetic tendency. Cure may also be simulated when a hypothyroid state is induced by the operation. A case of juvenile diabetes is cited to illustrate the palliative effect of myxedema developing in diabetes. When the basal metabolic rate of this child was restored to normal the previous diabetic state returned.

Special precautions are necessary when operating on patients with diabetes complicated by hyperthyroidism. The period of exacerbated toxicity which so often follows thyroidectomy is extremely dangerous. There is also considerable danger of provoking hypoglycemia in these patients since they may be peculiarly sensitive to overdoses of insulin. Hypoglycemic coma may be differentiated from other conditions of collapse by the fact that it is usually attended by a striking elevation of the blood pressure.

The phenomena exhibited by patients with diabetes combined with states of hyperthyroidism or hypothyroidism may be related to the general metabolic rate and thus may be explained without recourse to speculation as to a specific interdependence of thyroid and pancreas. It would seem that at lower metabolic rates the tissue cell is capable of utilizing a given amount of glucose with less insulin, and that with higher metabolic rates the requirement of insulin is disproportionately increased.

CARDIAC CAPACITY DETERMINED BY STANDARDIZED EFFORT

PRELIMINARY REPORT *

JOSEPH B WOLFFE, M D

PHILADELPHIA

A method of ascertaining the efficiency of the heart muscle is one of the greatest and most practical problems facing the general practitioner as well as the cardiologist. Late cases of decompensating hearts can be recognized easily. It is the early diagnosis of myocardial insufficiency that is of great value, for it is only at that stage that proper management may allay and frequently prevent decompensation. It would be a great error to recommend any one single method of investigation on which judgment may be based. Since the heart is one of the most susceptible indexes of health and mirrors the state of many other organs, it would be amiss to dissociate the study of the cardiovascular mechanism from the rest of the body, therefore, one must follow the accepted routine method of investigation in order to arrive at a fairly accurate diagnosis. Hence, a complete cardiovascular study should include a thorough history, a physical examination, roentgen-ray, electrocardiographic and polygraphic records, blood pressure and, last but by no means least, the cardiac response to effort.

Because of the present widespread conception that the electrocardiograph is the most infallible guide to the diagnosis of heart conditions, it is well to emphasize the fact for the benefit of those who are not acquainted with the instrument that it serves only as an adjunct, and although most valuable in recognizing disturbances in conductivity, it cannot in any way replace the previously mentioned methods of investigation. It is an accepted fact that frequently advanced pancardial changes electrocardiographically fail to show any appreciable abnormality.

Patients with injured hearts often present few signs on the usual physical examination while, on the other hand, some with marked abnormal physical signs recover without any treatment, or after reaching their three score and ten "die with it, but not of it." In the light of our present knowledge, we fully realize that it is not the extent of an endocardial lesion, or the loudness of a murmur, or the type of arrhythmia that is the determining factor of the actual state of the heart, but the condition of the heart muscle, its ability to stand up

* The response to exercise may be said to depend not only on the heart but also on the condition of the blood vessels, so that in speaking of the "cardiac response to exercise" we use the term "cardiac" as referring not only to the heart but also to the entire cardiovascular system.

under the load of daily physical strain, in other words, it is the amount of cardiac reserve force

After much experience and careful thinking, Sir Thomas Lewis, a great investigator and able teacher, writes as follows "Had systolic murmurs and modifications of the heart sounds never been discovered, the practice of medicine would have stood on a much higher plane than it does today" He regards the latter signs, and properly so, only as hints or guides to possible local mischief, but certainly does not attach the degree of importance that apparently is given them by the greater number of practitioners today

One is greatly impressed with the fact that even in the earlier works of Sir James Mackenzie, he constantly lays stress on the condition of the heart muscle and the amount of reserve force as a guide to the prognosis The relation between the cardiac force utilized during the hours of usual activity and the reserve force, which is called on only when additional strain is applied, is an important one It seems rational to think that any early cardiac pathologic condition which is not compensated for will diminish proportionately the cardiac reserve force Hence, any simple and accurate method by which the latter could possibly be determined should prove to be of untold value

Numerous tests have already been described by various investigators, many of which are practical with certain limitations The hopping test, which is used a great deal, varies greatly with the individual, with his mental attitude and his cooperation Many will not take it seriously, but consider it more or less as a joke, hence, the cooperation of the patient is poor and the importance and value of the test are greatly diminished Furthermore, such a test is not applicable in all cases, i e., a stout person would be at obvious disadvantages other than those which might justly be attributed to a myocardial condition

Running, swinging of dumb bells, lifting of weights, moving stairways, ergostats, stationary bicycles and other tests are subject to similar criticism Still, these are valuable in ascertaining the cardiac reserve force, provided the same test is repeated at intervals and the progress observed

INSTRUMENT FOR TESTING CARDIAC CAPACITY

It seems apparent that there is still room for a mechanism constructed for the purpose of subjecting a person to a predetermined amount of work and for a device connected with the mechanism for recording the work done In this way the person may be subjected to the same amount of work or more, if desired, at different intervals of time It is also important that the mechanism should be reliable and simple enough to be within the reach of any practitioner The instrument I am about to describe is a simple embodiment of these features

My belief in its reliability is based on the numerous experimental data compiled by my associates and myself, as well as on the fact that an apparatus of the same order has been, and still is, the most frequently used work measuring device of engineers all over the world

The salient features of the machine are shown in figure 1. A pulley is keyed to the shaft, which is rotated by the person to be exercised by means of handles rigidly connected to the shaft, as shown

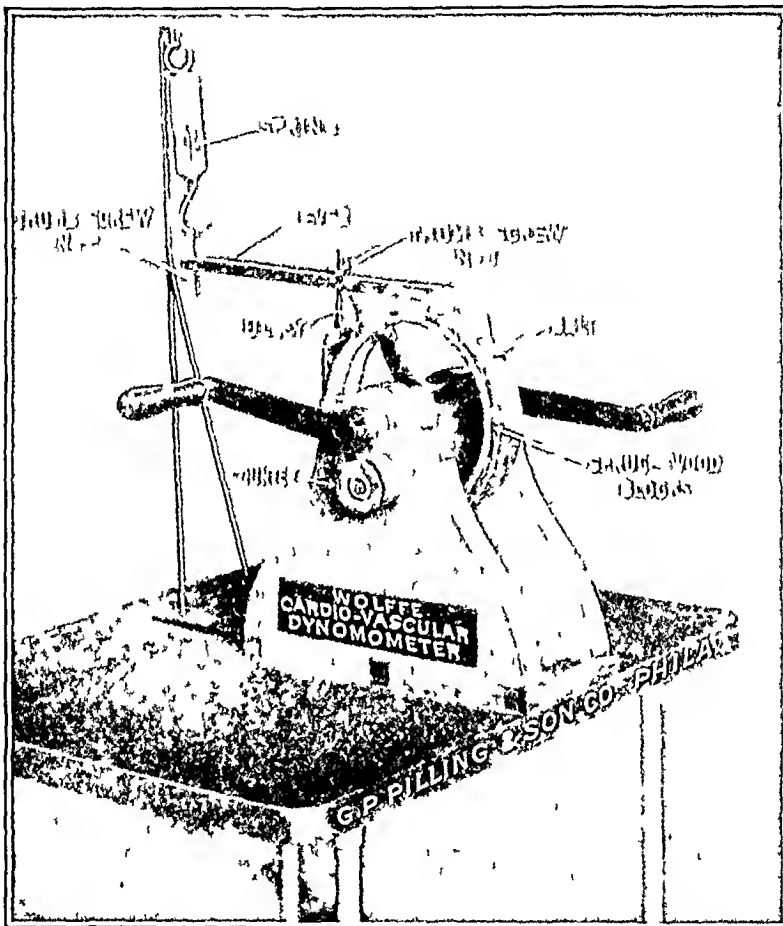


Fig 1—Cardiovascular dynamometer. Although this figure represents the machine I use, I am making many refinements at the present time, in conjunction with the George P. Pilling & Sons Company, which will greatly improve this model but not alter its general aspect.

The shaft revolves in bearings conveniently placed in the frame. A friction member, which is made up of a belt studded with wooden blocks, encircles the pulley. Blocks made of spruce wood have been found to give the best results. One end of the belt is nailed to the arcuate part of the lever while the other end carries a screw which fits into a perforation in the lever, thumb screw 1, and is held there by means of a thumb nut, thus giving the wide range of friction between the belt and the pulley.

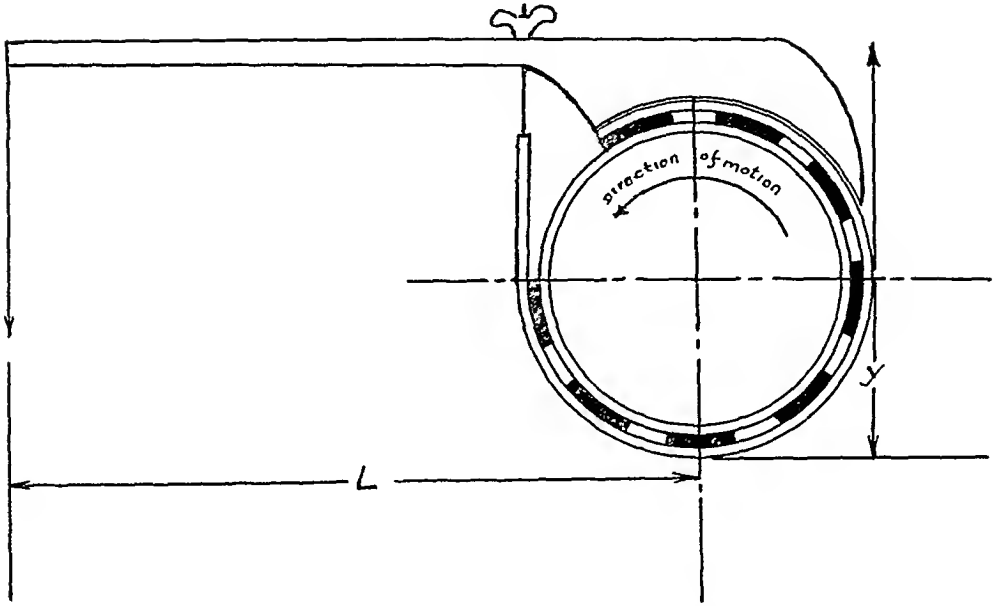


Fig 2—Cardiovascular dynamometer work chart

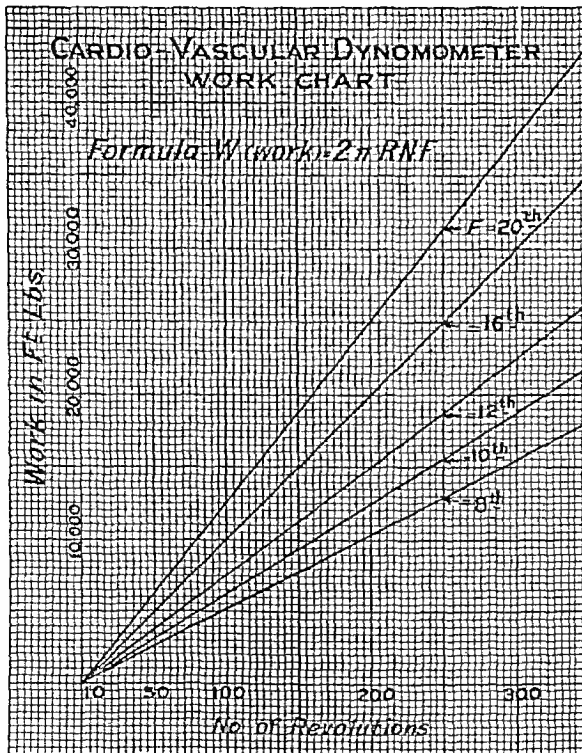


Fig 3—Work Chart

The friction between the belt and the pulley would ordinarily cause the belt and lever to turn together with the pulley. To keep the belt from turning, I connect the free end of the lever by means of a thumb nut, thumb screw 2, to the rigid scale, as shown. The scale is thus made to function as a measuring device of the force necessary to overcome the friction between the belt and the pulley, since it is evident that the tighter the belt is clamped down on the pulley, the greater

CARDIAC FUNCTIONAL TEST

No	5	Name	J.B.	Address	
Date		Age		Sex	
Occupation					
Diagnosis Negative physical findings					

Dyspnea **slight**

Palpitation **yes**

Cough

Cyanosis

Pain

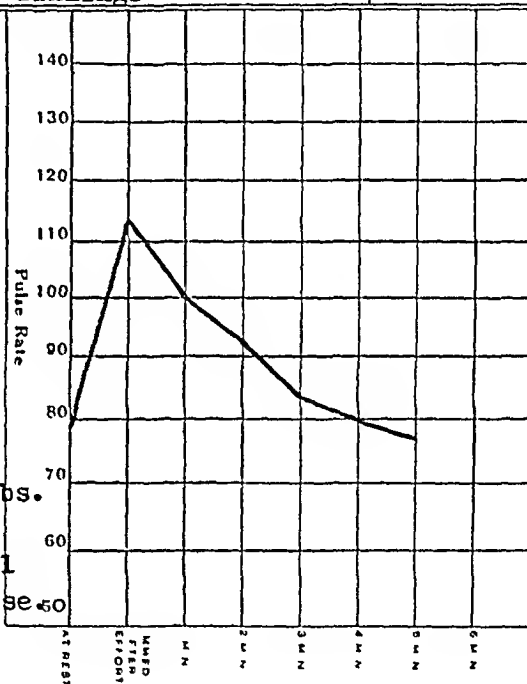
Other Remarks

Number of Revolutions **100**

Pounds of Pressure **10**

Total Amount of Work **6,000 ft. lbs.**

Result **Showing average normal cardiovascular response**



Subsequent Tests

Fig 4—Average functional response of 1,000 normal persons

will be the force necessary to keep the belt from turning with the pulley. As the tension of the belt is increased, the force registered will be increased, this causes the scale to be elongated, which in turn tilts the lever from its horizontal position. I compensate for this tilting by drawing thumb screw 2.

Thus far we have means for subjecting the person to be exercised to a predetermined strain while doing work. A established formula may be used. The derivation of this formula may be seen from figure 2.

Y indicates the radius of the pulley in feet, Z , the frictional force in pounds between the pulley and the blocks, F , the force in pounds recorded on spring balance, L , length of the brake arm in feet For the condition of equilibrium, i e, "horizontability" of the brake lever arm and by the law of moments for equilibrium, $Z \times Y = F \times L$ (1)

In one revolution, the frictional force Z is overcome through a distance equal to the circumference of a circle with a diameter $2Y$, i e, $2 \pi Y$

Hence, the work done in foot pounds during one revolution is $2 \pi ZY$ (2)

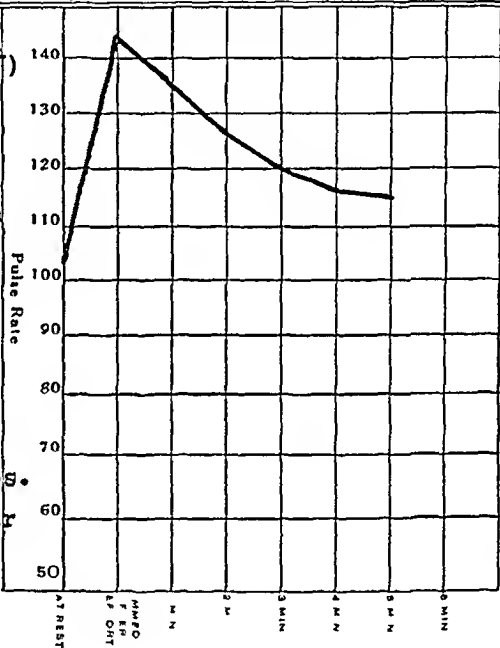
In n revolutions, the work done in foot pounds will be $2 \pi ZY n$ (3)

CARDIAC FUNCTIONAL TEST

No	2	Name	D.G.	Address					
Date	2-13-25	Age	24	Sex	male	Wt	145	Ht	
Occupation									
Diagnosis Myocardial degeneration (arteriosclerotic).									

Dysnea marked and prolonged
(2 min.)
Palpitation marked
Cough slight
Cyanosis --
Pain slight precordial pain
Other Remarks fatigue

Number of Revolutions 50
Pounds of Pressure 12
Total Amount of Work 3600 ft. lbs.
Result Impaired cardiovascular response to effort.



Subsequent Tests

Fig 5—Functional response in case of myocardial degeneration (arterio-sclerosis)

This formula could be readily employed provided some means could be used to obtain the frictional force Z But according to equation 1, the relation between ZY and FL is given as $ZY = FL$ Substituting the relation in equation 3, we have $2 \pi FLn$ and the formula to be used

For a given machine, the constants 2π and L can be combined in one constant k , thus the formula becomes

Work (foot pounds) = kFn

Further, if the value of F is kept constant, it can again be combined with the other constant k to form a new constant K The formula then becomes

Work (foot pounds) = Kn

This allows us to draw a chart (fig 3) with F as the ordinate and n as the abscissa on which the work done can be ascertained. If the force is kept constant, without resorting to calculation, curves for a number of different forces may be drawn on the same chart. Three such curves have been found sufficient in ordinary practice.

To determine the number of revolutions the person exercised has turned, I use the counter, actuated by a cam key to the shaft. The

CARDIAC FUNCTIONAL TEST

No	1	Name	F.L.	Address	
Date	2-15-25	Age	24	Sex	male
		Wt	147	Ht	
Occupation					
Diagnosis Neurocirculatory asthenia.					

Dyspnea **slight**

Palpitation **--**

Cough **--**

Cyanosis **--**

Pain **--**

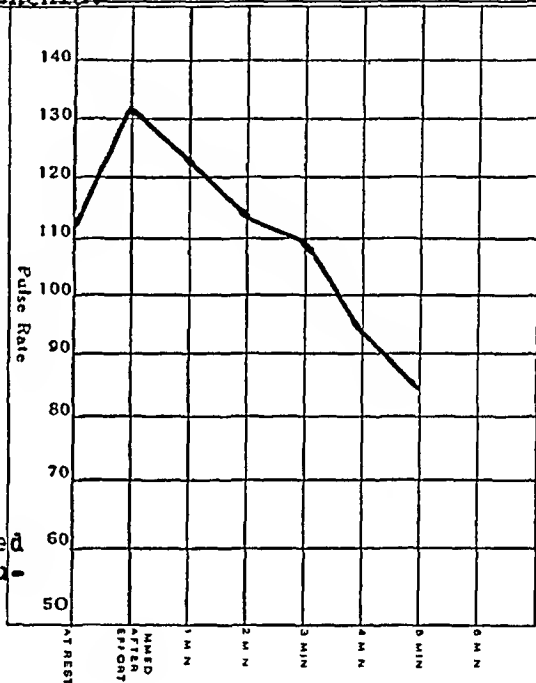
Other Remarks **muscle fatigue**

Number of Revolutions **50**

Pounds of Pressure **12**

Total Amount of Work **3600**

Result **Typical curve obtained in case of neurocirculatory asthenia.**



Subsequent Tests

This curve definitely shows that the pre-exercise elevation in pulse rate was due to a transient psychic tachycardia.

Fig 6—Functional response in a case in which there was much impaired cardiac reserve, showing the improvement in cardiac efficiency after adequate convalescent care.

rate at which the work is done can be regulated either by an attendant, who keeps time for the patient, or by means of a metronome, which has been found to be easily followed by the person exercised, and its use is conducive to much better results. If a metronome is used, the counter may be dispensed with since it is easy to obtain the number of revolutions, knowing the time the person was subjected to exercise,

1 e, if the metronome is set for thirty revolutions a minute, then the number of minutes exercised multiplied by the number of revolutions a minute gives the total number of revolutions. This may be done mentally, and the procedure of finding the work done is shown in figure 3

Work, from a physicist's point of view, is the overcoming of a force through a distance, and is measured by the product of the force

CARDIAC FUNCTIONAL TEST

No	384	Name	Z.M.	Address	
Date	2-13-25	Age	24	Sex	male
				Wt	145
				Ht	
Occupation					
Diagnosis	Mitral Regurgitation, left sided hypertrophy				

Dyspnea yes slight

Palpitation marked "

Cough -- --

Cyanosis -- --

Pain -- --

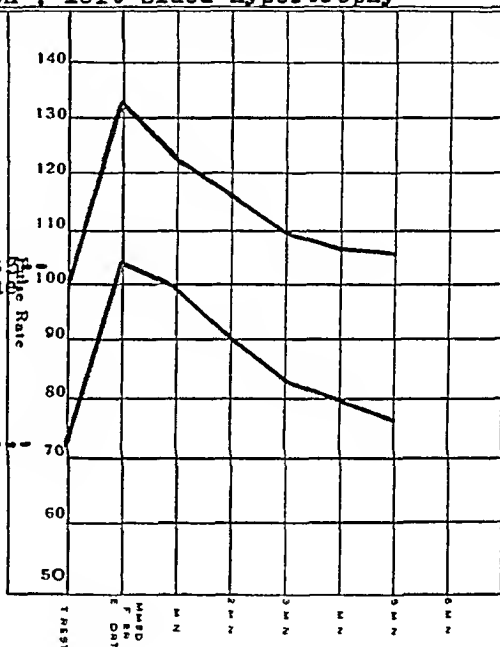
Other Remark fatigue slight fatigue

Number of Revolutions 50

Pound of Pressure 12

Total Amount of Work 3600

Result



Subsequent Tests

4-30-25

Curve #4 shows the myocardial response to effort after ten weeks of convalescent care, showing marked improvement in cardiac reserve

Fig 7—Functional response in case of mitral regurgitation and left sided hypertrophy

and the distance through which the force is overcome. With this instrument on hand, one can estimate the cardiac efficiency by the method either of Graupner or of Mendelsohn

(a) The Graupner method consists of taking the blood pressure before exercise and taking it again immediately after and at intervals until it returns to its preexercise pressure (b) The Mendelsohn

method, which we are using, consists of first taking the pulse while the patient is at rest. The patient is then subjected to a certain amount of work, individualized according to his age and physique. The pulse is taken again immediately afterward and at one minute intervals until it returns to its preexercise rate. After exercise the pulse rate is found to be elevated in every case, and if it is assumed the better the myocardium the sooner the pulse will return to normal, deductions can be made from the test as well as from similarly applied tests at subsequent comparative examinations.

Figure 4 shows the average response obtained in testing 1,000 normal persons.

Figures 5 and 6 illustrate the functional responses of persons of similar age and physique, but with different cardiac conditions, each showing a pulse record and symptomatic response frequently seen in the type of heart which it represents.

I should like to mention a few important clinical applications that this instrument would have for every practitioner.

1. The instrument would be a valuable adjunct in the diagnosis of myocardial degeneration. A patient with a poor myocardium is able to do only a comparatively small amount of work before he develops the characteristic symptoms of dyspnea, palpitation and precordial oppression.

2. If the amount of work required to produce these symptoms is noted at the first examination, the amount of work done at subsequent examinations before the onset of dyspnea, palpitation, etc., would determine the increase or decrease in myocardial power. This record is a valuable aid in determining the arrest or progress of the disease.

CONCLUSIONS

The practical determination of the efficiency of the myocardium is of paramount importance to every practitioner.

Such methods as foot hopping and dumb bell swinging have proved unsatisfactory, and the results are often misleading. Moreover, no one of these tests is applicable to all patients, nor is the information obtained conducive to the keeping of accurate records.

The use of an instrument such as that described above fulfils the requirements of simplicity in that it can be operated by a novice, and it is practicable in that the data obtained are of inestimable value in determining the cardiac efficiency of the patient, and records can be kept of the first and subsequent examinations.

Systematic use of the records obtained has proved an accurate guide in noting the progress of the disease.

As the patient improves and is able to perform more work without the production of symptoms, we have an indication to show him that he is convalescing. The encouragement this has produced is remarkable.

THE BASAL METABOLISM IN BERIBERI *

SEIZABURO OKADA

AND

EIICHI SAKURAI

TOKYO, JAPAN

The basal metabolism in beriberi was quite unknown until recent years. A systematic investigation on this problem was first attempted by us. The preliminary report ¹ was published at the same time as that of the basal metabolism of the Japanese, reported in a previous article. The conclusion was that the main part of beriberi shows a normal basal metabolic rate, except that in some cases, especially when paralysis or atrophy develops, a marked diminution is also to be observed.

Fleming ² studied the respiratory metabolism and blood chemistry of Filipinos and concluded that between two groups of Filipinos, one with a confirmed diagnosis of beriberi, the other surgical convalescents, no essential differences were found in the basal metabolism rate, respiratory quotient or blood chemistry.

As to the vital cause of beriberi, the opinions of various investigators are still diverse. Some workers attribute this disease to the effect of vitamin B deficiency, which seems most plausible, but this opinion has met strict contradictions. Therefore, it seems better to deal with this disease alone and not to touch on the vitamin deficiency disease in this article to avoid confusion.

OBSERVATIONS AND TECHNIC

The patients here studied were mostly outpatients and only some were ward patients. In all cases the symptoms had sufficiently developed to make a confirmed diagnosis of beriberi. The cases with complications or in which there were other diseases were carefully excluded. Some of the patients had already changed their usual dietary habits or were treated with medicines, while others were quite new patients who had not received treatment and who continued their usual nourishment and general habits of life (cases 16, 18, 30, 32, 33, 39, 41, 43 and 44).

The measurements were made by the method reported in the previous paper as used on normal subjects.

RESULTS

Physical Characteristics—The patients studied were all males ranging in age from 15 to 29, of whom twenty-two were from 15 to 19 and

* From the medical clinic of Prof. R. Inada, Imperial University of Tokyo.
1 Okada, S., Sakurai, E., Ibuki, T., and Kabeshima, H. *Ikaï Jiho* no 1479, Nov. 4, 1922, Japan M. World 3 102 (May) 1923.
2 Fleming, W. D. *J. Metab. Research* 4 105, 1923.

twenty-five from 20 to 29. The average height of the first group was 157.6 cm and of the second, 157.6 cm. The average weight was 51.5 and 54.5 Kg, respectively. The average weight of the patients more than 20 years of age was therefore much greater than that of normal subjects (2.65 Kg, 5.1 per cent) notwithstanding the fact that the average height of the former was somewhat less than that of the latter (4.3 cm, 2.6 per cent), a fact that may be attributed to the edema of the patients. The average surface area according to the Du Bois height-weight factor was 1.5 for the young patients and 1.54 square meters for the adults.

Clinical Observations—**Blood Pressure** All the ward patients were repeatedly examined. The systolic pressure ranged from 123 to 90 mm, the average being 107 mm, the diastolic pressure from 65 to less than 40 mm, so that it was often not measurable. The persistently low diastolic pressure with normal systolic pressure is the characteristic feature in beriberi. The pulse pressure was therefore usually greater than 50 mm and the celerity of the pulse usually was significant. With the decline of the disease the diastolic pressure rises after a while to the normal height.

Pulse Rate The pulse rate ranged from 50 to 120, the average being 77, which is distinctly higher than the average of normal subjects. In general when cardiovascular symptoms prevail, the pulse rate is high and especially when it threatens heart incompetence.

Respiration Rate The respiration rate was from 10 to 29, the average being 19, which is also distinctly higher than the normal value of 13. No parallelism between pulse rate and respiration rate is to be found.

Temperature The body temperature was from 35.6 to 37.4 C, in most cases being under 37 C. The climate, when the determinations were performed, was relatively hot, from May to October. This happened naturally as beriberi prevails in Japan in these seasons.

Heart The area of dulness of the heart was enlarged in most cases to both the right and the left side, roentgenologically and by pathologic anatomy this is proved to be due especially to the dilatation and hypertrophy of the right ventricle and auricle, with more or less marked accompaniment of the left. At the apex and at the left sternal margin the first sound was often hollow or a systolic murmur was recognized. The second pulmonic sound was almost always more or less accentuated. The crural and brachial sounds or murmurs were more or less pronounced.

Edema In most cases more or less edema was recognized, especially at the tibial edge, less often at the back of the foot. Pronounced general edema was in no case observed though creeping dropsy (not

TABLE 1—Metabolism Data in Beriberi Patients

Case	Age	Date	Height in Cm	Surface Area (Du Bois)		Respi- ration Rate	Carbon Dioxide per Minute	Oxygen per Minute	Respi- ratory Quotient	Calories for Each 2½ Hours	Calories per Square Meter (Du Bois)	Basal Metabolic Rate			Body Temper- ature, C
				Weight in Kg	Height-Weight Formula) Sq Meters							Calories per Square Meter (Du Bois)	Du Bois Standards, per Cent	Harris and Benedict Standards, per Cent	
1	15	5/25/22	156.2	18.9	1.16	80	184	247	0.74	1,678	47.9	+4.1	+18.2	+18.2	36.5
2	21	6/1/22	156.8	47.8	1.45	90	197	244	0.81	1,670	48.0	+4.3	+18.9	+18.9	36.6
		6/3/22		50.6	1.49	72	163	202	0.81	1,395	39.0	+1.3	-0.7	-0.7	37.0
3	27	6/7/22	146.2	46.3	1.49	75	177	211	0.84	1,166	41.0	+3.8	+4.3	+4.3	35.8
		6/9/22			1.49	80	161	204	0.79	1,409	40.8	-0.2	+0.8	+0.8	
4	16	8/1/22	152.3	47.2	1.36	84	150	197	0.76	1,332	40.8	+3.3	+0.4	+0.4	35.5
		8/3/22		44.0	1.37	82	154	185	0.83	1,289	39.2	-0.8	+1.0	+1.0	
5	22	8/4/22	156.6	44.6	1.37	78	173	187	0.92	1,328	40.4	-12.2	+0.2	+0.2	36.0
		8/14/22		66.8	1.38	66	169	190	0.90	1,351	40.8	-11.3	+1.3	+1.3	
6	16	8/16/22	161.0	66.5	1.67	50	146	187	0.84	1,214	30.3	-23.3	+1.3	+1.3	35.6
		8/22/22		64.3	1.67	58	160	173	0.85	1,310	32.7	-17.2	-24.1	-24.1	
7	24	8/9/22	153.5	54.7	1.64	56	151	178	0.85	1,240	31.5	-20.2	-21.5	-21.5	36.5
		8/12/22		53.2	1.57	66	182	206	0.88	1,151	38.5	-10.5	-4.3	-4.3	
8	25	8/16/22	158.5	53.8	1.54	60	183	193	0.94	1,101	37.9	-11.9	-6.4	-6.4	36.1
		9/1/22		47.8	1.43	64	161	193	0.93	1,397	37.8	-12.1	-7.1	-7.1	
9	18	9/5/22	163.0	58.3	1.42	84	148	204	0.70	1,411	41.1	+3.2	+6.1	+6.1	36.4
		9/10/22		54.1	1.59	100	170	206	0.72	1,394	40.9	+3.2	+5.3	+5.3	
10	21	9/6/22	169.5	57.0	1.57	105	144	183	0.76	1,523	39.9	+1.0	+2.1	+2.1	36.4
		9/10/22		37.1	1.60	84	168	175	0.79	1,266	33.6	-18.0	-15.1	-15.1	
11	18	9/8/22	159.0	57.0	1.60	84	179	233	0.93	1,255	38.3	-18.8	-16.9	-16.9	36.6
		9/19/22		37.1	1.31	60	149	206	0.77	1,570	39.1	-0.1	+0.8	+0.8	
12	19	9/25/22	153.0	45.5	1.45	66	170	181	0.82	1,308	41.6	+1.1	+4.5	+4.5	36.5
		9/25/22		45.3	1.39	90	155	191	0.97	1,569	15.1	+10.0	+11.8	+11.8	
13	24	9/28/22	161.0	44.6	1.38	60	151	181	0.81	1,321	39.6	+0.2	+2.2	+2.2	36.0
		9/28/22		54.8	1.77	88	163	181	0.83	1,285	37.9	-4.0	-2.2	-2.2	
14	17	10/1/22	159.0	55.5	1.58	60	166	236	0.83	1,643	43.6	+1.4	+0.9	+0.9	36.7
		10/1/22		50.2	1.50	60	163	202	0.84	1,411	39.2	-8.6	-1.8	-1.8	
15	17	10/4/22	163.3	49.6	1.49	64	168	185	0.80	1,411	39.2	-8.6	-1.8	-1.8	36.0
		10/8/22		66.1	1.72	68	163	185	0.80	1,411	39.2	-8.6	-1.8	-1.8	
16	16	10/9/22	161.5	66.3	1.72	68	163	185	0.80	1,411	39.2	-8.6	-1.8	-1.8	36.3
		10/9/22		66.1	1.72	68	163	185	0.80	1,411	39.2	-8.6	-1.8	-1.8	
17	22	10/22/22	156.5	55.5	1.57	68	163	185	0.80	1,411	39.2	-8.6	-1.8	-1.8	36.3
		10/23/22		54.6	1.53	110	160	223	0.81	1,603	12.7	-0.2	+5.2	+5.2	
18	18	10/27/22	120	55.5	1.52	90	165	219	0.84	1,447	38.4	-0.7	+0.3	+0.3	36.8
		11/2/22		44.6	1.38	84	165	219	0.70	1,531	11.3	+0.7	+3.5	+3.5	
19	19	11/3/22	155.0	44.6	1.38	84	165	219	0.70	1,531	11.3	+0.7	+3.5	+3.5	36.5
		11/1/22		44.6	1.38	98	162	219	0.70	1,492	40.9	-0.2	+1.9	+1.9	
20	21	11/16/22	155.0	54.7	1.52	90	161	209	0.77	1,437	43.4	+5.8	+9.4	+9.4	36.5
		11/17/22		54.3	1.52	78	178	227	0.70	1,521	41.7	+5.1	+6.7	+6.7	

21	26	11/23/22	159 0	56 3	1 56	94	19	192	270	0 71	1 808	48 3	+22 3	+23 7	36 7
		11/24/22		56 4	1 57	53	21	190	238	0 80	1 639	43 5	+10 2	+12 1	36 5
22	17	11/25/22	150 5	56 4	1 57	104	24	192	287	0 67	1 895	50 3	+27 3	+29 6	36 6
		5/10/23		47 3	1 47	90	20	173	210	0 82	1 462	42 0	-2 3	+7 0	38 3
23	20	5/12/23		47 2	1 45	87	19	163	196	0 83	1 364	39 2	-8 8	+0 7	36 5
24	21	5/25/23	157 0	64 5	1 63	78	25	198	249	0 79	1 710	43 7	+6 6	+7 3	33 9
		7/19/23	167 5	60 9	1 69	64	23	167	233	0 75	1 521	37 5	-5 1	-4 9	36 8
25	26	7/20/23		61 2	1 69	61	23	178	197	0 90	1 407	34 7	-12 1	-12 3	36 4
		7/19/23	161 5	60 3	1 64	55	21	187	206	0 81	1 468	37 3	-3 9	-3 9	36 5
26	22	7/21/23		58 9	1 63	49	19	193	217	0 89	1 522	38 9	+0 8	+0 8	
		7/19/23	149 5	52 5	1 46	90	19	219	263	0 82	1 843	52 6	+32 1	+32 9	
		7/20/23		51 8	1 45	82	19	190	198	0 96	1 430	41 1	+4 0	+3 7	
27	19	7/21/23		51 5	1 45	72	23	171	179	0 96	1 284	36 9	-6 6	-6 5	37 4
		7/22/23	165 5	60 7	1 67	108	18	222	234	0 91	1 679	41 9	+2 2	+4 9	37 3
		7/23/23		60 3	1 67	86	14	203	250	0 85	1 735	43 3	+5 6	+8 8	36 6
28	19	7/26/23	162 0	54 6	1 57	76	23	162	228	0 71	1 537	40 8	-0 5	+2 4	36 5
29	21	7/26/23	162 2	54 3	1 57	78	22	144	208	0 71	1 394	37 0	-6 8	-7 0	36 5
		7/27/23		54 9	1 57	72	19	175	211	0 83	1 387	36 8	-7 0	-7 0	36 4
30	23	7/26/23	156 5	49 8	1 48	76	20	191	206	0 83	1 471	41 4	+4 8	+6 7	36 7
		7/27/23		49 2	1 47	64	18	165	210	0 79	1 461	41 4	+4 8	+6 5	36 0
31	23	7/29/23	159 3	60 2	1 62	68	13	182	216	0 84	1 505	38 7	-2 0	-2 6	36 0
		7/30/23		59 8	1 61	63	14	178	211	0 81	1 484	38 4	-2 8	-3 0	36 3
32	21	7/20/23	152 5	48 5	1 43	80	19	156	192	0 81	1 328	38 7	-2 0	-2 0	37 0
		7/30/23		48 6	1 43	77	15	135	191	0 81	1 318	38 4	-2 8	-2 8	36 6
33	19	8/ 2/23	159 0	58 0	1 59	60	21	179	214	0 83	1 496	39 2	-4 5	+2 3	36 7
34	23	8/ 3/23	155 5	53 1	1 51	74	14	164	206	0 80	1 421	39 2	+0 3	+0 3	36 9
35	16	8/ 2/23	150 5	46 7	1 39	114	16	158	222	0 71	1 491	44 7	-0 7	+10 1	37 3
		8/ 3/23		46 6	1 39	89	16	154	217	0 71	1 465	43 9	-4 5	+8 3	36 8
36	20	8/ 5/23	162 0	55 7	1 59	86	15	183	236	0 71	1 729	45 3	+14 6	+19 4	36 9
		8/ 6/23		55 6	1 59	60	12	166	235	0 71	1 587	41 6	+5 3	+10 0	36 4
37	23	8/ 5/23	162 7	51 6	1 54	120	16	188	233	0 75	1 722	46 6	+17 9	+20 0	37 4
		8/ 6/23		51 4	1 54	80	15	180	237	0 76	1 623	43 9	+11 4	+13 3	36 8
38	20	8/ 9/23	159 5	55 2	1 56	108	25	208	265	0 79	1 820	48 6	+18 5	+23 3	37 0
		8/10/23		54 1	1 55	110	26	218	265	0 82	1 811	49 5	+20 7	+24 9	37 0
39	19	8/ 9/23	160 0	53 3	1 54	76	30	172	232	0 74	1 571	42 5	+3 6	+6 7	36 4
40	22	8/ 9/23	164 5	44 1	1 39	67	18	194	232	0 84	1 348	40 4	+2 3	+3 9	36 8
		8/10/23		43 7	1 38	60	17	163	192	0 85	1 314	40 6	+2 7	+4 0	36 5
41	23	8/10/23	158 0	64 7	1 66	80	22	206	226	0 91	1 606	40 3	+2 0	+0 9	36 5
42	18	8/12/23	154 5	50 6	1 47	67	19	176	231	0 70	1 693	48 0	+11 6	+19 7	36 3
		8/13/23		50 2	1 47	60	18	158	237	0 70	1 521	43 2	+0 5	+8 2	37 1
43	26	8/12/23	155 5	59 5	1 58	76	16	185	247	0 75	1 684	44 4	+12 4	+21 4	36 6
44	19	8/12/23	145 5	41 7	1 29	77	20	167	186	0 89	1 313	42 4	+3 4	+5 9	36 8
		8/13/23		41 7	1 29	74	19	151	174	0 87	1 226	39 6	-3 4	-1 1	36 1
45	18	8/30/23	165 0	55 2	1 60	54	13	201	217	0 98	1 574	41 0	-4 6	+2 9	36 5
		8/31/23		54 6	1 60	52	11	213	214	0 94	1 536	40 0	-7 0	+0 9	36 3
46	19	8/30/23	149 5	57 1	1 39	69	10	189	208	0 93	1 448	43 4	+5 8	+8 5	37 1
47	19	8/30/23	159 2	56 1	1 57	74	19	204	230	0 89	1 620	43 0	+4 9	+7 5	36 9
		8/31/23		56 0	1 57	61	20	208	234	0 89	1 654	43 9	+7 1	+0 9	36 9

* All males

TABLE 2—*Mam Clinical Aspects*

Case	Heart			Accentuation of the Second Pulmonic Sound	Crural Sound	Edema	Knee Jerks	Achilles Reflexes	Hypesthesia	Remarks
	Right Border (Absolute Dulness)	Left Border (Absolute Dulness)	Nipple line							
1	Right sternal margin		Nipple line	+	Murmur +	+	—	—	Legs +	Paralysis of legs ++, tenderness of calf muscles +, Chaddock +
2	Normal		Normal	+	Murmur +	+	—	—	Legs +	Paralysis of legs +, tenderness of calf muscles +, cyanosis +
3	Midline		Just inside of nipple line	+++	+++	+	—	—	Legs +, lips +	Brachial sound +, cyanosis +, main diet, rice, August 17, died of heart incompetence
4	Left sternal margin		Nipple line	+++	+++	++	—	—	Legs +, right hand +, lb doubt +	Brachial murmur +, weakness and numbness of legs +
5	Midline		Half finger inside of nipple line	—	—	—	Normal	Normal	Legs +, hands +	Tenderness of legs +++, numbness of lips and legs +, urine protein trace, indleau +
6	Midline		Inside of nipple line	+, di vided	+++	—	Very active	Active	Legs +	Brachial sound weak, numbness of legs and arms ++, urine, indleau +
7	Right sternal margin		Just inside of nipple line	—	++	—	—	—	Legs +	Brachial sound weak, paresthesia +, weakness and numbness of legs +, palpitation +, tenderness of calf muscles +
8	Right sternal margin		Nipple line	+	++	++	—	—	+	Brachial sound +, numbness of legs +, urine protein, trace
9	Right sternal margin		One finger out side of nipple line	+++	++	++	—	—	Legs +	Tenderness of calf muscles +, weakness of legs ++
10	Midline		Nipple line	++	++	+++	—	—	++	Paresthesia +, paralysis of, Chaddock +
11	Midline		Inside of nipple line	+	+	—	—	—	+++	Numbness and paralysis of legs ++
12	Normal		Normal	+++	++	+	—	—	Legs +, finger +	Brachial murmur +, tenderness of calf muscles +, numbness of legs +
13	Normal		Normal	++	++	+	—	—	Legs +	Paresthesia +
14	Normal		Nipple line	+	++	++	Very active	Very active	Legs +	Numbness and weakness of legs +, tenderness of calf muscles +, Chaddock +
15	Midline		Inside of nipple line	+	+	++	—	—	Legs +	Numbness of legs +, tenderness of calf muscles +
16	Midline		Just inside of nipple line	+	+	+++	Active	Active	+	Tenderness of calf muscles +, Chaddock +
17	Midline		Just inside of nipple line	++	+	+	Very active	Very active	Legs +	Paresthesia +, tenderness of calf muscles +, Chad
18	Midline		Nipple line	+	+++	++	—	—	Legs +	Brachial sound +, palpitation and dyspnea on move- ment +
19	Midline		Nipple line	++	+	+++	—	—	Legs +	Paresthesia +
20	Midline		Nipple line	+	Murmur +	+++	—	—	Legs +	Tenderness of calf muscles +, Chaddock +
21	Midline		Somewhat out- side of nipple line	++	+	++	—	—	Legs +	Numbness and paresthesia of legs +

22	Right sternal margin	+	Murmur +	++	Normal	Normal	Legs +	Numbness of legs +, tenderness of calf muscles +, urine protein, trace, indican +
23	Midline	++	Murmur ++	+++	—	—	+	Weakness of legs +, palpitation on movement +
24	One finger right of left sternal margin	+	+	+	—	—	Legs +	Brachial sound +, numbness of legs and fingers +
25	Normal	+	Murmur ++	+	—	—	Legs +	Brachial sound +, tenderness of calf muscles +, palpitation on movement +
26	Right sternal margin	++	Murmur ++	+++	—	—	+	Numbness of legs
27	Midline	++	Murmur ++	+	—	—	+	Brachial sound + tenderness of calf muscles +, liver palpable two fingers under the rib arch
28	Midline	+	+++	+	—	—	+	Brachial sound +, numbness of legs and fingers +, Chaddock +
29	Right sternal margin	++	+++	+	Very weak	—	+	Brachial sound +, tenderness of calf muscles +
30	Right sternal margin	++	+++	—	—	—	++	Brachial sound weak +, weakness of legs +, tenderness of calf muscles +, Chaddock +
31	Right sternal margin	—	Murmur ++	++	—	—	Legs +	Brachial sound very weak +, numbness of legs +, tenderness of calf muscles +
32	Normal	+	+++	+	Active	Weak	+	Brachial sound +, numbness of finger tips and legs +, tenderness of calf muscles +
33	Midline	+++	++	—	Right nor mal, left —	Right nor mal, left —	—	Brachial sound +
34	Midline	++	+	++	Normal	Weak	++	Brachial sound +, weakness of legs +, liver palpable two fingers under the rib arch, Chaddock +
35	Right sternal margin	++	+++	++	—	—	—	Brachial sound +, tenderness of calf muscles +, Chaddock +, liver palpable two fingers under the rib arch
36	Midline	++	+++	+	Active	Active	Legs +	Brachial sound +, numbness of legs +
37	Midline	++	+++	+++	—	—	+	Brachial murmur +, numbness of fingers and legs +, tenderness of calf muscles +, Chaddock +
38	Right sternal margin	++	+++	+++	—	—	+	Palpitation on movement +, Chaddock +
39	Right sternal margin	+++	++	+++	Weak	—	+	Brachial sound +, tenderness of calf muscles +, weakness of legs +, palpitation on movement +
40	Midline	++	+++	++	Normal	Weak	+	Brachial sound +, tenderness of calf muscles +, weakness of legs +, urine protein, trace, indican +
41	Right sternal margin	++	+++	+	Very active	Active	+	Brachial murmur +, Chaddock +, weakness of legs +
42	Right sternal margin	+++	+++	+	Very active	Active	Legs +	Brachial sound +, urine protein, trace
43	Midline	++	+++	+	Active	Active	+	Brachial murmur +, weakness of legs +, urine protein, trace
44	Normal	++	+++	+	Weak	Weak	+	Brachial murmur +, numbness of fingers and legs +, urine protein, trace
45	Normal	+	+++	—	Very weak	Very weak	+	Brachial murmur +, numbness of finger tips and legs +
46	Midline	++	++	+	Very weak	—	+	Brachial sound +, urine protein, trace
47	Midline	++	++	+	—	—	+	Brachial sound +, numbness of legs +

readily proved by pressing the skin, but in which there is increase in body weight, which decreases with diuresis) was often proved to exist by means of diuretics

Nervous System In general disturbances of motility, sensibility, etc., prevail, especially at the under part of the body. Hypesthesia and paresthesia are the common feature in beriberi. Weakness of the under limbs, which sometimes grows to a real paralysis, is often observed, the patients walk as if they walk in a muddy marsh. The knee jerks and Achilles reflexes are often absent, but in some cases, especially at the beginning of this disease, there are increased and very active tendon reflexes. The skin reflexes also are often absent or weak. Tenderness and hardness (Chaddock) of the muscles of the under limbs, especially of the calf muscles, are often observed. Abnormal softness of the calf muscles is not the common feature. In none of our cases was the contracture of the ankle joints in consequence of the peroneal paralysis marked. Hypesthesia and paresthesia also were proved to exist at the upper limbs and around the mouth. Edema and paresis of the glottis was sometimes recognized by the hoarseness of the voice.

Respiratory Quotient The respiratory quotient ranged from 0.67 to 0.98, the average being 0.82, which coincides with the value of normal subjects.

Basal Metabolism Comparing the basal heat production predicted by means of the Harris and Benedict formula with that actually measured, we have found that 87.3 per cent of cases and 80.4 per cent of measured times show deviations less than ± 15 per cent from the standards, and 86.2 per cent of cases and 74.7 per cent of measured times are within ± 10 per cent. A comparison of the heat production per square meter of body surface per hour with the Aub and Du Bois standards shows 92.5 per cent of cases and 88.5 per cent of measured times to be within ± 15 per cent, and 86.2 per cent of cases and 71.2 per cent of measured times to be within ± 10 per cent of the standards. Nine fresh cases in which treatment had not been given showed normal basal metabolism, except one with a somewhat high value. The cases with a basal metabolism higher than $+15$ per cent of the standards have always shown a pulse rate of more than 80, i. e., the involvement of the cardiovascular system has always been significant. Case 21 showed on the first and third days a very high basal metabolism and high pulse rate, while on the second day there was an almost normal basal metabolism with quiet pulse. Case 26 also showed on the first day a very high basal metabolism and high pulse rate, on the succeeding days a normal basal metabolism with lower pulse rate. We are not ready to explain the very low metabolism in cases 5 and 9. It is not certain whether this occurred as the result of this disease or because of some unknown reason as we sometimes find this condition in normal subjects.

The clinical symptoms in these cases are not sufficient to explain this low metabolism. On the other hand, we have seen some cases that assumed a marked diminution of the basal metabolism in the course of this disease. These patients are apt usually to show distinct paralysis, especially of the under limbs, and atrophy of the muscles. Table 3 gives examples of such cases.

The report of the cases in table 3 follows.

TABLE 3—*Cases in Which Paralysis Developed in the Course of the Disease*

Case	Date	Height in Cm	Weight in Kg	Surface Area (Du Bois Height- Weight Formula) Square Meters	Pulse Rate	Respi- ration Rate	Calories for Each 24 Hours	Calories per Square Meter (Du Bois)	Basal Metabolic Rate		Body Tem- pera- ture, C
									Du Bois Stan- dards, per Cent	Harris and Benedict Standards, per Cent	
1	5/29	156.6	38.9	1.35	88	19	1,675	51.7	+12.4	+30.4	37.8
	6/17		44.9	1.41	84	13	1,408	41.6	-9.5	+3.0	36.7
	6/29		40.5	1.36	82	20	1,211	37.1	-19.3	-7.3	36.2
	7/10		42.7	1.38	95	19	1,275	38.5	-16.3	-4.5	36.4
	7/14		43.6	1.39	62	18	1,201	36.0	-21.7	-10.9	
	7/17		39.0	1.35	56	17	1,175	36.8	-20.0	-8.6	36.7
	7/29		37.5	1.31	66	23	1,056	33.6	-27.0	-16.4	36.5
	8/5		37.6	1.31	68	19	1,160	36.9	-20.0	-8.4	36.5
2	7/27	162.5	51.5	1.54	75	21	1,408	38.1	-7.1	-3.1	36.5
	7/29		51.8	1.54	72	16	1,353	36.6	-10.8	-7.1	36.6
	8/22		47.4	1.48	62	14	1,016	28.6	-30.2	-27.2	36.4
	8/29		48.1	1.49	66	21	1,109	31.0	-21.5	-21.7	36.4

Patient 1 was 14 years and 5 months of age, patient 2, 19 years and 6 months.

In case 1 the vitamin B medication given consisted of intravenous injection of extract of rice bran (oryzanin), June 20, 10 cc, July 1, 10 cc, July 13, 10 cc, July 14, 10 cc, July 15, 5 cc, and July 16, 5 cc. From July 23 extract of rice bran, 10 Gm per day, was given regularly until the patient left the hospital.

In case 2, the vitamin B medication consisted of 40 Gm of spelzon (a Japanese vitamin B proprietary preparation), July 9, 26 Gm of spelzon, July 10, and 3 Gm of extract of rice bran (oryzanin) July 11. From July 12, 10 Gm of extract of rice bran per day was given regularly until the patient left the hospital.

REPORT OF CASES

CASE 1—J. S., a houseboy, aged 14 years and 5 months, was admitted to the hospital, May 25, 1922, complaining of dyspnea, oppression in the chest and some fever (from otitis media).

There was nothing special in the family history. He had had measles when 6, had been twice vaccinated. He had had severe stomach and intestinal disease when 3. Since then he had always been somewhat weak, but had had no particular disease. He had had severe beriberi of the cardiovascular type when 13.

Since the beginning of this month he complained of heaviness of the legs and palpitation which became severer on movement. He was somewhat constipated, the appetite was unchanged. The evening of May 19 about 9 he suddenly became pale and complained of nausea and tension of the abdomen, but no pain. A physician diagnosed the case as beriberi. The patient stayed in bed, but dyspnea and the oppression in the chest continued. Now and then pain was felt at the cardiac region and the left hypochondrium. The face was swollen but there was no edema at the tibial edge. Since then he had had hypesthesia of the legs, fingertips, at the circumference of the umbilicus, and in the hips. Motility was quite normal. The voice had become somewhat hoarse.

Examination showed the pupillary reflexes normal. The teeth and tonsils were in good condition. The lungs were intact. There was no enlargement of the heart, the second pulmonic sound was divided and somewhat accentuated, the second aortic sound was divided and the systolic murmur was audible. Crural and brachial sounds were recognized. There was tenderness of the abdomen under the umbilicus. The liver was not palpable. The upper limbs were

intact with normal tendon reflexes. The knee jerks and Achilles reflexes were negative. Weakness of the legs was present but no paralysis. Urinalyses showed indican positive, no protein and no casts.

The heart was enlarged in the course of observation, June 20, the area of absolute dulness reached to the right sternal margin, to the upper edge of the third rib and the left nipple line, the area of relative dulness was a half finger to the right side of the right sternal margin, to the upper edge of the second rib and the left nipple line. The walk had become awkward and paralysis of the peroneal nerve was evident at this time. It was especially marked from June 26 to July 20, after which it became better. By August 5 the walk had become nearly normal. From June 19 to 29 the patient took somewhat less nourishment but the weight of the body was higher at this time (owing to the edema), at other times he always took an adequate amount of food to maintain vigor. The blood pressure on admittance was 100 systolic, 30 diastolic, and June 20, 120 systolic, 45 diastolic. Many times from June 20 and regularly after July 23 a large amount of vitamin B medication was tried. The basal metabolism was consistently low from June 29 to August 5.

CASE 2—K. K., a stationer's attendant, aged 19 years and 6 months, was admitted to the hospital, July 23, 1922, complaining of weakness, palpitation on movement and pulsation at the epigastrium, oppression in chest, dyspnea and edema.

He had had measles when a child, was twice vaccinated. Since the end of June he had suffered weakness and edema of the legs, since about the tenth of July, palpitation on movement and pulsation at the epigastrium.

Examination showed the pupillary reflexes normal. The lungs were intact. The area of absolute cardiac dulness was from the midline to the upper edge of the fourth rib and two fingers inside the nipple line, the area of relative dulness from the right sternal margin to the upper edge of the third rib and one finger inside the nipple line. The second pulmonic sound was somewhat accentuated. The crural sound was clapping, the brachial sound audible. The knee jerks and Achilles reflexes were negative, there was tenderness of the calf muscles, the walk was normal. The blood pressure was 134 systolic and under 40 diastolic.

Beginning August 9, a large amount of vitamin B medication was tried, still by the end of August the paralysis of the under limbs, especially of the peroneal nerve, had become noteworthy. This was accompanied by hypesthesia of the legs and the circumference of the umbilicus. The food intake was normal. The basal metabolism at the end of July was normal and at the end of August distinctly low.

These two cases showed distinct diminution in the basal metabolism during the course of the disease. The marked feature appearing parallel with this diminution was the paralysis of the under limbs. We have also found such diminution in the basal metabolism in other diseases with paralysis or atrophy.

SUMMARY

- 1 In most cases of beriberi quite normal values in the basal metabolism and respiratory quotient were found.
- 2 When cardiac incompetence threatened an increased basal metabolism was observed.
- 3 When paralysis and atrophy became remarkable a diminution in the basal metabolism occurred.

THE USE OF INSULIN BY MOUTH[†]

H R MILLER, M D

NEW YORK

The parenteral use of insulin has obvious disadvantages, consequently, a method for the oral use of insulin would be valuable. The authors cited below show how frequently this attempt has been made and with what unsatisfactory results.

Harrison¹ tried to administer insulin in alcoholic solution. He gave, by mouth, from 20 to 40 units of insulin, and seems to have obtained a fall in blood sugar in an occasional case. Similarly, Winter² administered insulin in a 20 per cent alcoholic solution by mouth (stomach tube) to rabbits. He, too, observed a drop of the blood sugar in some instances (rabbits, also in man).

Sansum, Blatherwick and others³ concluded, after repeated trials of administration by mouth, that insulin was efficient by the hypodermic route only. Orally they gave as much as twenty-five times the subcutaneous dose to patients and to experimental animals. Murlin, Sutter, Allen and Piper⁴ gave large amounts of slightly acidified insulin extract. Their hope was that some of this material would fortuitously leave the stomach and thus reach the circulation before gastro-intestinal enzymes would affect the insulin. An insulin precipitate with protein was also tried. Furthermore, they administered insulin in alcoholic solution to normal rabbits and to partially depancreatized dogs. Their results for animals and human beings were not constant and, therefore, unsatisfactory. Salen⁵ confirmed this opinion. Finally, Sansum and his co-workers made use of capsules and tablets coated with phenyl salicylate. Capsules containing insulin preparations were dipped in phenyl salicylate and enclosed in larger gelatin capsules. Further trial of this method was urged as offering a possibility for a practical means of giving insulin by mouth. They stressed the value of putting within the capsule, together with the insulin preparation, some substance that would help to delay the destructive action of trypsin. Torrey⁶ obtained a

[†] From the medical service at the New York Post-Graduate Hospital

1 Harrison, G A. *Brit M J* **2** 1204 (Dec 22) 1923

2 Winter, L B. *J Physiol* **58** 18 (Oct) 1923

3 Sansum, W D, Blatherwick, N R, Smith, Florence H, Long, M Louisa, Maxwell, L C, Hill, Elsie, McCarty, Ray, and Cryst, J H. *J Metab Research* **2** 641 (May-June) 1923

4 Murlin, J R, Sutter, C C, Allen, R S, and Piper, H A. *Endocrinology* **8** 331 (May) 1924

5 Salen, Ernst. *Acta med Scandinav* **60** 1, 1924

6 Torrey, E W. *Am J Electroth & Radiol* **41** 319 (Oct) 1923

rather striking depression of the blood sugar level in diabetic patients from the oral use of pigs' pancreas extracts (fresh) He experimented with four different kinds of extracts and described the process of preparation of each Rather indifferent results were published by Mendel, Wittgenstein and Wolffenstein⁷ with a dry insulin preparation given by mouth

The student of the subject is impressed with the vagaries of the effects from the oral use of insulin Apparently, at times, there is a flicker of hope that insulin by mouth is effective, as evidenced in a marked lowering of the blood sugar level, but it is well to remember in this connection that the diabetic patient, as a rule, is being starved during the experiment, and that during starvation the blood sugar may fall remarkably of its own accord Mosenthal⁸ has shown this One of his diabetic patients had a fall of 80 mg in blood sugar from 9 a m to 5 p m (started at 220 mg and fell to 140 mg), in another patient the blood sugar decreased from 315 mg at 9 a m to 263 mg at 5 p m (a fall of 52 mg) Spontaneous descent of the blood sugar level in the diabetic patient, accordingly, may be responsible for a share of the fall in blood sugar noted in all experiments cited above With this in mind our patients tested received no food before or after the use of insulin by mouth, in order to prevent confusion from a possible postprandial hyperglycemia as a complicating factor It is, of course, important to know whether the preparation taken by mouth is absorbed from the stomach or intestines and particularly whether this is necessary when some form of capsule method is used The roentgen ray would prove valuable in ascertaining the course and fate of opaque capsules

We attempted to give the usual stock Lilly preparation of insulin in 95 per cent alcohol solution or absolute alcohol by mouth Our method was to use not more than 3 minims of insulin, regardless of the strength, in not less than 1 cc of alcohol (either absolute or 95 per cent solution) placed in the ordinary gelatin capsule, which was then dipped in keratin solution The keratin solution was a 7 per cent glacial acetic acid preparation We discovered early that if the alcoholic concentration was reduced to less than 75 or 80 per cent, osmosis took place through the gelatin capsule wall This may explain the failure of those investigators who gave insulin in alcoholic solutions of low strength

Patients received their usual diet the day before insulin was administered by mouth but fasted after supper, throughout that night and the next day until the end of the experiment Blood was taken for a blood sugar reading then insulin by mouth administered immediately, and no food given until the termination of the experiment A group of nine

7 Mendel, B., Wittgenstein, A., and Wolffenstein, E. *Klin Wchnschr* 3 470 (March 18) 1924

8 Mosenthal H O. *Tice's Practice of Medicine*, p 69

nondiabetic patients received insulin by mouth under these precautions and by this method Table 1 illustrates the failure of these nondiabetic patients to show any appreciable drop in blood sugar

It is difficult to understand why, if insulin by mouth has any effect at all, it failed to influence the blood sugar of these nondiabetic patients. We are therefore compelled to believe that insulin by mouth—certainly in nondiabetic patients—is not absorbed into the general circulation at

TABLE 1—*Absence of Any Appreciable Effect on the Blood Sugar of Nondiabetic Patients from the Use of Insulin in Strong Alcoholic Solutions Administered by Mouth*

Case	Fasting Blood Sugar	Insulin by Mouth	Continued Fast	Final Blood Sugar	Change in Blood Sugar
1	138 mg	64 units	2 hours 35 minutes	108 mg	—30
2	93 mg	40 units	5 hours 30 minutes	116 mg	—12
3	92 mg	96 units	4 hours	94 mg	+ 1
4	88 mg	48 units	7 hours	89 mg	— 7
5	84 mg	48 units	5 hours	85 mg	— 3
6	86 mg	96 units	5 hours	77 mg	— 7
7	63 mg	40 units	8 hours 30 minutes	99 mg	+13
8	57 mg	40 units	4 hours	65 mg	+ 2
9	83 mg	48 units	4 hours	78 mg	+21
			4 hours 25 minutes	96 mg	+13

TABLE 2—*Influence of Insulin in Strong Alcoholic Solution Given by Mouth, on the Blood Sugar Level of Diabetic Patients*

Case	Sex*	Age, Years	Fasting Blood Sugar	Units of Insulin	Continued Fast	Drop of Blood Sugar to	Change in Blood Sugar, Mg	Fasting Blood Sugar	Units of Insulin by Mouth, Units	Continued Fast	Drop of Blood Sugar to	Change in Blood Sugar, Mg
1	♂	68	167	0	6 hours	143	—24	230	64	7 hours 55 min	153	—77
2	♀	51	188	0	6 hours	176	—12	172	96†	7 hours	144	—28
3	♂	38	232	0	7 hours	208	—24	356	264†	8 hours	214	—142
4	♀	58	168	0	4 hours 5 minutes	150	—18	248	96	7 hours	156	—92
5	♀	54	128	0	6 hours	111	—17	174	64	5 hours	125	—49
6	♀	49	143	0	4 hours 5 minutes	118	—25	166	48	7 hours	103	—63
7	♂	36						137	96	2 hours	50	—87
8	♂	52						167	64	6 hours	141	—26
9	♀	42						204	64	5 hours	150	—54
								231	96	7 hours	158	—73
								283	96	7 hours	202	—81

* In this table, ♂ indicates male, ♀, female

† For these large doses highly concentrated preparations of insulin were employed in order to keep the total amount of alcohol as low as possible

all, or at most in insufficient quantity. In any case, even if absorbed it does not affect the blood sugar level.

Table 2 demonstrates the effects of insulin given by mouth, in the same manner, to diabetic patients. The blood sugar level nearly always fell after such use of insulin and in some instances at least this decline was much greater than we would expect starvation alone to accomplish. Most of the patients listed were put through a "control day" to note the effect of starvation alone on blood sugar. In six such diabetic patients,

starved only, the average drop in blood sugar was 20 mg over a period of from four to seven hours. This is contrasted with the results in diabetic patients, the same six (plus three others), who received insulin by mouth while starving and in whom the average blood sugar drop was 68 mg over an interval of time that ranged from two to eight hours.

An important consideration is the height of the blood sugar level at the commencement of the experiment. For instance, the fasting blood sugar of case 5, table 2 (chart 1), could not be expected to show as marked a decline either from starvation alone or from starvation plus insulin by mouth, as in case 2 (chart 2) in which the fasting blood sugar, on one of the days of the experiment, was 356 mg. Yet despite all

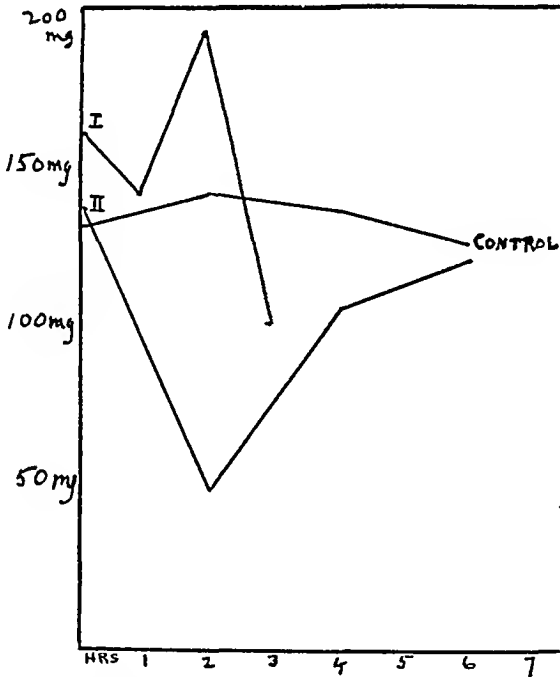


Chart 1—Blood sugar curves of diabetic patient 5. The control test (starvation only) was made Dec 18, 1925, while 48 units of insulin in 95 per cent alcohol solution was given by mouth, Nov 28, 1925, and 96 units, under similar conditions, Dec 21, 1925. The records in detail are

48 Units of Insulin (I)			96 Units of Insulin (II)			Control—No Insulin		
A	M	8 40	A	M	8 30	A	M	8 30
		Blood sugar			Blood sugar			Blood sugar
		(fasting) 166 mg			(fasting) 137 mg			(fasting) 128 mg
		8 45 Insulin by mouth			8 35 Insulin by mouth			
		9 40 Blood sugar 142 mg			10 30 Blood sugar 50 mg			10 30 Blood sugar 143 mg
		10 40 Blood sugar 182 mg			12 30 Blood sugar 119 mg			12 30 Blood sugar 136 mg
		11 40 Blood sugar 103 mg	P	M	2 30	P	M	2 30
					Blood sugar 121 mg			Blood sugar 126 mg

critical inferences, one may indicate that the use of insulin by mouth, as administered by the method outlined above, seemingly lowered the blood sugar level in diabetic patients. Unfortunately, we could carry out no roentgen-ray studies to determine the fate of the keratin coated capsules in the gastro-intestinal tract. The examination of the stools for their recovery was not always satisfactory.

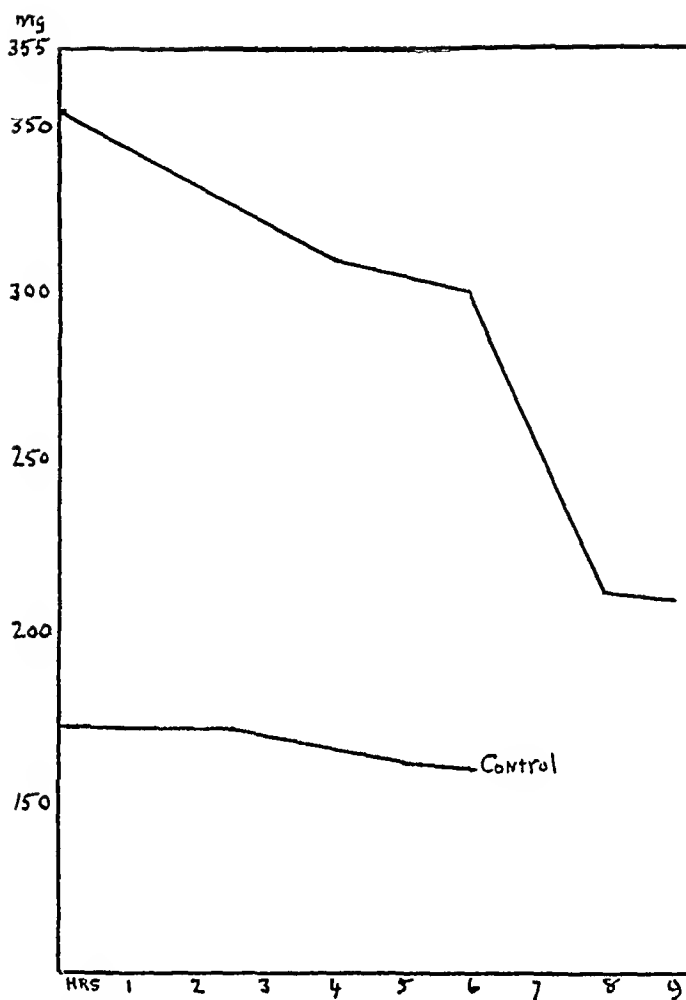


Chart 2—Two blood sugar curves in diabetic patient 2. The control test (starvation only) was performed, Dec 22, 1925, while 264 units of insulin in 95 per cent alcohol solution was given by mouth, Jan 6, 1926.

264 Units of Insulin					Control—No Insulin				
A	M	8 00	Blood sugar (fasting)	356 mg	A	M	8 30	Blood sugar (fasting)	188 mg.
		8 05	Insulin by mouth						
		10 00	Blood sugar	336 mg			10 30	Blood sugar (fasting)	188 mg.
		12 00	Blood sugar	314 mg			12 30	Blood sugar (fasting)	178 mg
P	M	2 00	Blood sugar	302 mg	P	M	2 30	Blood sugar (fasting)	176 mg
		4 00	Blood sugar	214 mg					

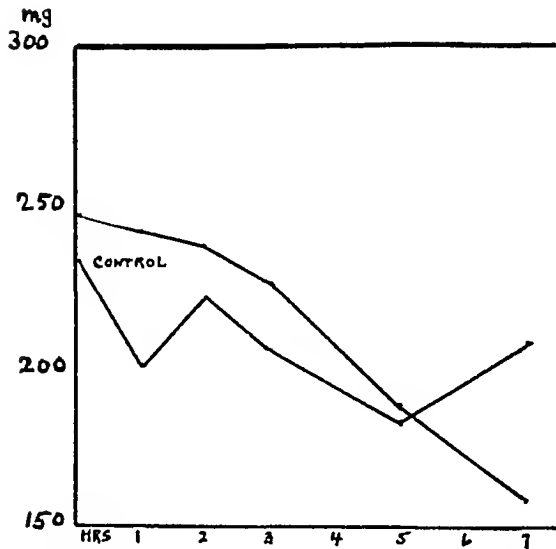


Chart 3—Comparison of the fall in blood sugar in diabetic patient 3 The control test (starvation only) was carried out, Dec 28, 1925, and the experiment of giving by mouth 96 units of insulin in 95 per cent alcohol solution, under similar conditions, was performed, Dec 29, 1925 The records in detail are as follows

96 Units of Insulin					Control—No Insulin				
A	M	8 30	Blood sugar (fasting)	248 mg	A	M	8 30	Blood sugar (fasting)	232 mg
		8 35	Insulin by mouth						
		9 30	Blood sugar	212 mg			9 30	Blood sugar (fasting)	204 mg
		10 30	Blood sugar	238 mg			10 30	Blood sugar (fasting)	234 mg
		11 30	Blood sugar	225 mg			11 30	Blood sugar (fasting)	203 mg
P	M	1 30	Blood sugar	188 mg	P	M	1 30	Blood sugar (fasting)	184 mg
		3 30	Blood sugar	156 mg			3 30	Blood sugar (fasting)	208 mg

CONCLUSIONS

We are not in a position as yet to offer this method of insulin administration for the treatment and control of diabetic patients. It appears likely, however, that insulin given in absolute alcohol or 95 per cent alcohol solution (total solution not to be below 85 per cent alcohol), within keratinized capsules, lowers the blood sugar level of diabetic patients. As already suggested, we should prefer to learn the fate of these keratin coated capsules after they are swallowed in order to ascertain the amount of insulin which may enter the circulation and to gauge such factors as absorption and dangers. We report our results, at this time, however, so that carefully controlled experiments may be assembled on a larger scale and thus lead to a definite evaluation of any merit this method may possess.

THE GROWTH OF THE LONG BONES IN CHILDHOOD

WITH SPECIAL REFERENCE TO CERTAIN BONY STRIATIONS OF
THE METAPHYSIS AND TO THE RÔLE
OF THE VITAMINS^{*}

H A HARRIS, M B

ST LOUIS

INTRODUCTION

The mainspring of medical research is the interpretation of the phenomena of disease in terms of disordered physiology. The widest gap in the search for this interpretation is seen in diseases of the bony, muscular and blood vascular systems. The innumerable systems of classifying diseases of bone, teeth, muscle and blood vessels indicate that either the clinical and pathologic data or the normal developmental processes have not been elucidated. Our knowledge of the anatomy and physiology of bone is limited. On the one hand, little is known of the nerve supply and lymphatic supply of this tissue. Attempts to interpret the function of the periosteum have produced a series of conflicting views from Hunter¹ and Duhamel,² Cheselden and Haller, Ranvier and Sharpey to Tilley, Macewen³ and Gallie and Robertson⁴. The origin of the osteoblast is still undecided, though recent workers such as Stump⁵ and Fell⁶ tend to regard the chondroblast, osteoblast and osteoclast as closely related descendants of the primitive connective tissue cell. The experimental work in rickets has led to a number of "schools" in which the calcium, phosphorus, vitamin A and vitamin X have been successively brought into the limelight. The purely graphostatical laws of the structure of the bony lamellae presented by Meyer⁷ and Wolff⁸ have been shown by Jansen⁹ to be

^{*} From the Institute of Anatomy, University College, London, and Washington University Medical School

1 Hunter, John. The Works of John Hunter, London, 1835, vol 4, p 317

2 Duhamel. Sur le developpment et la crue des os, Mém Acad d Sc, 1742, p 497, and 1743, p 187

3 Macewen, W. The Growth of Bone. Observations on Osteogenesis, Glasgow, 1912

4 Gallie, W E, and Robertson, D E. The Repair of Bone, Brit J Surg 7 211 (Oct) 1919

5 Stump W C. The Histogenesis of Bone, J Anat 59 136-154, 1925

6 Fell, H B. The Histogenesis of Cartilage and Bone in the Long Bones of the Embryonic Fowl, J Morphol & Physiol 40 417-460, 1925

7 Meyer, H. Die Architectur der Spongiosa, Reichert and Dubois, Raymond's Arch f Anat, 1867

8 Wolff, Julius. The Law of the Transformation of Bones, 1892

9 Jansen, Mark. On Bone Formation, Leiden, 1920

inadequate The relationship of the size of the medullary cavity to the size and character of the contained bone marrow is still a mystery, although this involves the two tissues, bone and marrow, which are characterized by the maximum power of physiologic growth, repair and rapid hypertrophy in the human economy Similarly, the muscular system, forming 43 per cent by weight of the healthy adult, is subject to a group of diseases in which no correlation has, as yet, been found between the normal physiologic and the varied pathologic processes

First, it is proposed to describe in detail a case that illustrates the actual process of bone growth in the long bones of a child over a period of two years, with the registration of the effects of severe illness thereon Secondly, the whole problem of the genesis of bony striations in the metaphyseal region of the long bones will be discussed

PART I

AN ILLUSTRATIVE CASE

A girl, aged 2 years and 8 months, was admitted to the hospital with measles and severe bronchopneumonia There was a history of bronchopneumonia at 16 months and of marked liability to colds Evidence of consolidation of the lung persisted for nine weeks and there was marked bronchiolectasis with clubbing of the fingers, spasms nutans developed and persisted for three weeks There was no history or evidence of rickets, the child was discharged with a persistent cough and a slight evening temperature, and was supervised by the social workers as a possible case of tuberculosis The child was well nourished and more than the average weight, but suffered a great deal from cough The home conditions were such that the child spent a considerable portion of her time indoors Eight months later, the child was readmitted with whooping cough and severe bronchopneumonia, temperature 105, pulse 160 and respirations 80 per minute The signs were most marked over the left lung and the right base After a stay of five weeks in the hospital, she was discharged in much the same condition as formerly, but the decreased movement of the left side of the chest was more marked and there was a difference of 1 inch (2.5 cm) in the measurement of the left and right semiperimeter of the chest The cough was paroxysmal and the sputum copious

One year later, the child was admitted with a severe bronchopneumonia, palpable spleen, clubbed fingers, temperature 104.5, pulse 150 and respirations 60 The cardiac area was definitely enlarged as regards visible pulsation, the heart was enlarged to percussion, and Traube's space was diminished by the splenic enlargement The skin over the chest was somewhat transparent, the nails were brittle, the clubbing of the fingers was marked On discharge the child presented the picture of bronchiolectasis with moderate emphysema No laboratory evidence of the presence of tuberculosis was obtained at any time, the Wassermann reaction was negative, nor was there any sign of rickets Thus, in three successive years the patient had been subjected to three distinct illnesses (1) measles with bronchopneumonia, (2) whooping cough with bronchopneumonia and (3) bronchopneumonia

A routine roentgenogram of the chest and epiphyses of the child while attending the outpatient clinic after the second illness showed the presence of certain lines of dense bone near the end of the diaphyses These lines of dense bone were most marked in the lower limb, were clearly seen at the shoulder and wrist, and were least obvious at the elbow Accordingly, as no reference to the existence of these lines apart from rickets had been seen, roentgenographic examination was made of the long bones of the child at successive dates over a period of two

years One of the roentgenograms taken after the second illness shows a line of dense bone as a transverse striation in the diaphysis about 1 cm away from the epiphyseal line of the lower end of the femur, upper end of the tibia and lower end of the tibia There is another dense striation much nearer the epiphyseal line, in close proximity to the metaphysis These two lines were regarded as being formed during the first and second periods of acute illness At the lower end of the tibia there were faint traces of transverse striations more proximally placed in the diaphysis and these were regarded as the residue of the attack of bronchopneu-



Fig 1—Leg bones showing transverse bony striations

monia which the child suffered at 16 months, and of the "severe colds" in babyhood, which were probably accompanied by some bronchopneumonia

After three roentgenograms had been taken over a period of thirty-one weeks, the patient had another severe attack of bronchopneumonia and a roentgenogram was taken during the convalescence period seven weeks after the onset of the attack The roentgenogram, figure 1, showed a third series of lines of dense bone formed near the metaphysis almost at the ends of the diaphyses

Roentgenograms were taken over a period of two years and the outlines of the roentgenograms were transferred to paper by pricking the outlines through a print on to a bristol-board and joining the pin pricks by a line. Figure 2 is a series of eight drawings from roentgenograms (marked *A* to *H*) taken over this period. The outlines of all eight roentgenograms were reduced to a uniform scale, the day, month and year are written below and the numbers 1, 2 and 3 indicate the transverse striations formed during the three successive acute illnesses

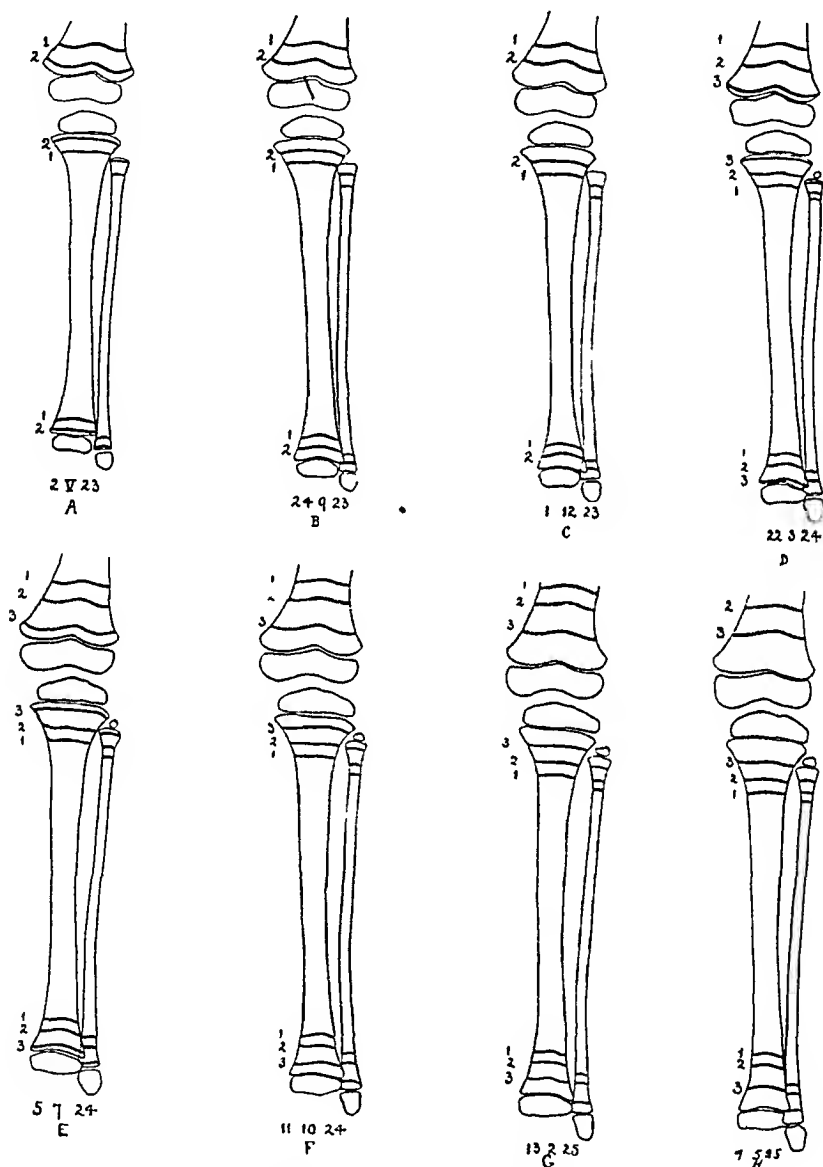


Fig 2—Outline of roentgenograms over a period of 106 weeks, the lines are numbered for the first, second and third periods of cessation of growth during the three acute illnesses

Figure 3 was constructed from these roentgenograms, the abscissae representing the time in weeks of the various illnesses, the ordinates the length of the diaphysis, and the position of the transverse striations being numbered 1, 2 and 3. The dense lines show the superior and inferior limits of the diaphysis of the tibia and their gradual divergence gives the actual amount of growth at each end in centimeters and the gradient gives the rate of growth. The faint lines indicate

the transverse striations for the first two illnesses in the case of roentgenograms *A*, *B* and *C*, and for all three illnesses in the subsequent roentgenograms *D* to *H*

Since the transverse striations remain steadfastly parallel and equidistant, we now have a convincing proof that there is no interstitial growth in the shaft of the tibia and all growth in length takes place by the apposition of new bone to the ends of the diaphysis at the metaphyses. Furthermore, the periods of slow growth from *A* to *B* and from *D* to *E* correspond to periods immediately following the illness, and these are followed by periods of rapid growth from *B* to *C*, and from *E* to *F* when the child was subjected to increased fresh air, sunlight and extra feeding during two successive autumns

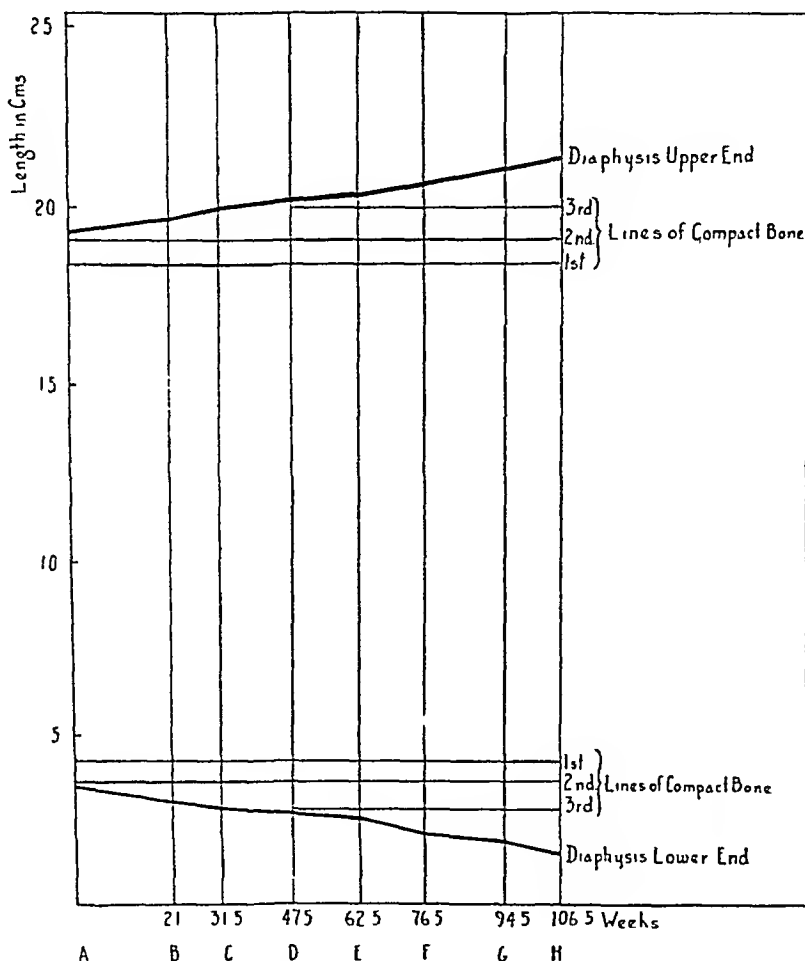


Fig 3—The growth in length of the tibia over a period of two years

It can be seen from figure 2 that the distance between the lines at the lower end of the femur is different from that at the two ends of the tibia. Over a period of 106 weeks the total increase in length at the lower end of the femur is 2.1 cm, at the upper end of the tibia 1.9 cm, and at the lower end 1.8 cm. That is to say, the most active growth takes place at the lower end of the femur, and the growth at the upper end of the tibia has been slightly in excess of that at the lower end of the tibia, in conformity with the accepted view that growth at the knee is a little more active than growth at the ankle and hip. The distances between the three lines at the lower end of the femur and at the two ends of the tibia also confirm this.

THE EXPERIMENTS OF HUNTER AND DUHAMEL

Hunter,¹ to ascertain whether the long bones are elongated by the interposition of new bone in the interstices of the old, performed the following experiment. He bored two holes in the tibia of a young pig, one near the upper end, and the other near the lower, the space between the holes was exactly 2 inches (5 cm). A small lead shot was



Fig. 4—Multiple transverse striations in the shaft of the tibia of a girl, aged 14 years

inserted into each hole. When the bone had increased in length by the growth of the animal, the pig was killed and the space between the two shots was still found to be exactly 2 inches.

In the Palmer edition of the works of John Hunter there is an erroneous account of the lead shot and silver stylet experiments of

Duhamel This chapter in the history of bone growth is adequately discussed by Keith,¹⁰ and as Keith says, "Duhamel has been unfortunate in his commentators" The experiments of Hunter and Duhamel in both pigs and birds show clearly that there is no intercalated growth in length in the diaphysis of the long bone This fact is adequately confirmed by the observations over a period of two years on the tibia of our young patient There is no justification for the statement of Macewen¹¹ "Interstitial growth occurs in the diaphyses of long bones, contributing slightly to increase in length"

The lead shot experiment by Hunter on the tarsometatarsus of the fowl has been frequently adduced as evidence of interstitial growth Keith¹⁰ has shown both that Hunter probably understood the phenomenon of "drag on the periosteum" and that Humphrey described the phenomenon clearly in the explanation of the oblique course of the nutrient canal In this respect it is interesting to note that the transverse striations tend to become less distinct toward the periphery, i e., immediately beneath the periosteum The "drag on the periosteum" accounts for the fact that the striations are more rapidly obliterated in close proximity to the periphery of the bone As Flourens¹² said, "Mais si, d'une part, des molécules nouvelles sont incessamment déposées, si, d'autre part, des molécules anciennes sont incessamment resorbées, il ya donc mutation continuelle de la matière"

PART II

BONY STRIATIONS IN THE METAPHYSIS

A History—The early roentgenograms of this patient were shown at a meeting of the Association of Anatomists in London in the summer of 1923 and, some time later, Professor Policard of Lyon called my attention to various reports in the French clinics of "stries osseuses dans le metaphysaire" Tillier¹³ in 1920 described certain diaphyseal lines in roentgenograms of the long bones of children, lines that were straight, very slightly sinuous, and of regular thickness He used these lines as a justification for the view that the metaphysis had as individual an evolution as the diaphysis and the epiphysis and considered in detail the particular pathologic conditions found After examination of cases of rickets, tuberculosis, osteomyelitis and synostosis of the inferior extremities of the tibia and fibula, Tillier concludes that the line of dense bone represents a region of accessory epiphyseal cartilage

10 Keith, Arthur *Menders of the Maimed*, London, 1919, p 212

11 Macewen Footnote 3, p 198

12 Flourens, M J F *Recherches sur le developpement des os*, Paris, 1842, p 98

13 Tillier, R *Une particularité de Structure du Squelette Infantile Révélée par la Radiographie*, Lyon Chir **17** 433-488 (July-Aug) 1920

which later undergoes marked ossification and condensation and represents the union of primitive diaphysis with metaphysis. The frequency of juxta-epiphyseal fractures, especially at the inferior extremity of the radius and ulna, is attributed to bending strains in the region of these lines.

Mouchet¹⁴ in 1921 described such lines in girls from 13 to 15 years of age who complained of vague pains in the lower limbs which were attributed to "growing pains." One of the girls presented three transverse striations at the inferior extremity of the right and left tibia and fibula. A single striation was seen at the lower end of the femur and at the upper end of the tibia but not at the upper end of the fibula. The cases described by Tillier were characterized by a single striation through the metaphysis, though he refers to a description by Bioca of multiple lines in cases of rickets. Mouchet points out that the existence of three striations in the case of his girl patient negatives the view of Tillier, for three such lines could not, each and severally, indicate the union of two skeletal segments, the metaphysis and diaphysis. Also in Mouchet's case there was no history or evidence of rickets.

Bopp and Ulrich¹⁵ in 1922 described two transverse striations in the inferior extremities of the bones of the left and right leg in a patient aged 46. The striations were situated at the line of the epiphyseal union and 1 cm proximal. Faint lines also were seen at the upper extremity of the tibia and fibula, but there was no trace of these lines in the bones of the upper limb. These lines were not related to any traumatism, and no pathologic antecedents could be found, the Wassermann reaction was negative. Bopp and Ulrich incline to the view of Tillier that such lines represent a condensation in cartilage "rests" in the metaphysis.

In 1923 Hertz and Lévy-Lebhar¹⁶ saw in the roentgenogram of the lower end of the tibia in a girl of 8 years seven lines, of which four were very distinct and the upper three less so. They point out the improbability of seven such parallel lines being accessory epiphyseal cartilages or of such lines marking two bony zones. One year later, in 1924, Di Maclaure¹⁷ presented a case with several striations in the long bones of a patient in whom there was no evidence of rickets. He discusses in detail the various views put forward and shows that none of the cases are adequately explained by either of the three theories put forward by previous investigators. Maclaure points out that if addi-

14 Mouchet, A. Stries transversales des metaphyses du femur, du tibia, et du perone, Bull et mem Soc de chir de Paris **47** 178-179, 1921.

15 Bopp and Ulrich. Stries metaphysaires chez un adulte de 46 ans, Bull Soc anat de Paris **92** 676-677, 1922.

16 Hertz and Levy-Lebhar. Sur les stries juxta-epiphysaires des os longs, Bull Soc anat de Paris **93** 260-261, 1923.

17 Maclaure. Stries osseuses transversales sur plusieurs os chez le même sujet, Bull Soc anat de Paris **94** 446-447, 1924.

tional strains were a factor in the etiology, one ought to find such striations in the os calcis, which is very susceptible to slight changes of use and disuse and registers the various forms of bony atrophy with facility and rapidity. The rachitic etiology is untenable as so many cases have been described in patients of various ages who present no history or evidence of rickets. These lines have not been reported in Madelung's disease, with marked rachitic changes at the distal extremity of the radius nor in cases of genu valgum.

B The "Line Test" of Park and Howland—In 1921 Park and Howland¹⁸ described the "line test" for healing rickets. After treatment with cod liver oil, changes are detected by roentgenogram about the end of the third or fourth week, occasionally a little before. In the case of two children who died six days and twelve days after the beginning of cod liver oil medication there was no appreciable deposition of calcium salts on microscopic examination. The line gradually becomes thicker and thicker in cases of healing rickets and is more dense than other parts of bone. The pathologic studies of Schmorl have shown that in the process of healing the deposition of calcium salts takes place first in the cartilage on the epiphyseal side of the transitional zone, i. e., in the place where the lime salts would have been deposited had there been no rickets. The deposition in this locale is the cause of the linear shadow on the roentgenogram. Gradually, the material in the transitional zone is transformed into bone and becomes infiltrated with calcium salts. From two to three months are necessary for the completion of the process of repair and even then the trabeculae of the repaired zone show certain irregularities in the arrangement of the trabeculae.

In 1923 Evans¹⁹ described certain cases of acute rickets in late childhood and adolescence, and he says, "The cartilage of conjugation may show a linear ossification bisecting the cartilage into two thinner disks. It is an early sign of recovery and is known as the line test."

C Starvation in Rickets—McCollum²⁰ and his co-workers observed healing of rickets in starvation. Ten rats with well developed rickets were starved to death over periods of time lasting from three to five days. In each case the line test of calcification was positive both on roentgenographic and histologic examination. The addition of 2 per

18 Park, E. A., and Howland, J. The Radiographic Evidence of the Influence of Cod Liver Oil in Rickets, *Bull. Johns Hopkins Hosp.* **32** 341-344 (Nov.) 1921.

19 Evans, T. L. Acute Rickets in Late Childhood and Adolescence, *Brit. M. J.* **2** 1212-1213, 1923.

20 McCollum, E. V., Simmonds, S., Shipley, P. G., and Park, E. A. Studies on Experimental Rickets. XV. The Effect of Starvation on the Healing of Rickets, *Bull. Johns Hopkins Hosp.* **33** 31-33 (Jan.) 1922.

cent cod liver oil to the ricket producing diet also gave a positive line test in five days. McCollum suggested that starvation liberates from the tissues an organic factor or factors which cause calcium deposition to occur in the cartilage. This he ascribed to the increase of phosphorus in the blood. McCollum regards his experiments as "furnishing the first anatomical proof of the beneficial effect of starvation on the animal body. The good effects of fasting are given a new meaning, because the organism is able to adapt itself to pathogenic distortions of normal metabolic ratios when the burden of carrying on exogenous metabolism is removed. Since the starving body is capable of readjusting abnormal relations within itself it is easy to understand the benefit derived by a diabetic from occasional hunger days, and why it is that the wasted athreptic infant does not develop rickets."

McCollum as a protagonist of starvation is dismissing the fact that his so-called beneficial effect of starvation is really cessation of growth and heralds death. The athreptic child is too busy trying to hold on to life to grow, and not growing—develops no rickets. The fact that he develops no rickets may be equally well ascribed to the beneficial effect of athrepsy.

The recent spectacular assertions of de Bosanyi²¹ to have cured rickets by hitherto undescribed antirachitic substances require careful examination from the point of view of cessation of growth. De Bosanyi asserts that he has cured rickets by the administration of hemoglobin, cystine, epinephrine and pilocarpine. Van Leersum previously said that he had cured rickets by hematoporphyrin. De Bosanyi treated rachitic rats by 5 per cent chlorophyll solution and showed healing of their rickets. He says, "But these animals, although they did not starve, lost a great deal of weight and died in two weeks." It is submitted that here again the bony striation which is regarded as that of healing rickets is really only a manifestation of cessation of growth and athrepsy.

D Rickets in Relation to Cessation of Growth—Pappenheimer²² fed rats on a ricket producing diet

When, however, as exceptionally happens, no growth has occurred during the earlier weeks, the rachitic lesions are apt to be poorly developed. We have also observed that rapid loss of weight, especially when associated with diarrhea, favors the deposition of calcium. This is comparable to the effect of complete starvation as described by McCollum, Simmonds, Shipley and Park.

21 De Bosanyi, Andor. Studies of Certain Hitherto Undescribed Antirachitic Substances, Bull Johns Hopkins Hosp 38 72-74 (Jan) 1926

22 Pappenheimer, A. M. Experimental Rickets in Rats. VI. The Anatomical Changes Which Accompany Healing of Experimental Rat Rickets Under the Influence of Cod Liver Oil or Its Active Derivatives, J Exper Med 36 336 (Sept) 1922

In the ribs of athreptic nonrachitic rats on a deficient dietary, or in which failure of growth had occurred because of infection, Pappenheimer found that the matrix of the zone of preparatory calcification was as densely calcified as in the normal bone "In old animals, after the cessation of epiphyseal growth, or in larger animals, in which arrest of growth is artificially brought about by dietary deficiency, such as lack of fat soluble A, the trabeculae atrophy or become fused into a transverse plate of bone extending across the cartilage" It is submitted that this also is a bony striation indicating cessation of growth

Hess, McCann and Pappenheimer,²³ feeding rats on a diet deficient in vitamin A, describe a thin continuous plate of fully calcified bone, limiting the cartilage and fusing with the calcified matrix The skeletal changes in no way resemble those of rickets, and the authors state that "this is what might be expected in view of the stationary or declining weight and arrest of growth" Many of these rats had acute suppurative infections of the alimentary, respiratory and urogenital tracts The skeletons of such rats showed no gross changes whatsoever

E The Transverse Striations in Scurvy—Transverse striations in the shafts of the long bones have been described in scurvy by Lehdorff²⁴ Dense bands of shadow, of variable width, have been described as "trummerfeldzone," often several in number and crossing the shaft like "strips of embroidery" The "trummerfeldzone" lies on the epiphyseal side of the metaphysis, on the diaphyseal side of the metaphysis a light zone has been described as "geiustmarkzone" These lines of increased earthy deposition and bands of decreased earthy deposition have been regarded as specific of scurvy Such concentric lines of dense bone formation have also been described in the epiphyses and os calcis

Tozer²⁵ has described the histologic findings in scurvy and has depicted the shortening of the rows of the cartilage cells and of the trabeculae In figure 16 in her article describing a case of chronic scurvy, Tozer shows the typical transverse striation of condensed bone The transverse striation is seen only in those cases of chronic scurvy which have presented cessation of growth over some period of time

F Fusion Lines—The fusion lines between the epiphyses and diaphyses of the long bones have recently been described by Cope,²⁶ and

23 Hess, A F, McCann, G P, and Pappenheimer, A M Experimental Rickets in Rats II The Failure of Rats to Develop Rickets on a Diet Deficient in Vitamin A, *J Biol Chem* **47** 395-409 (July) 1921

24 Lehdorff, H Zur Kenntniss des Morbus Barlow, *Arch f Kinderh* **38** 161-167, 1904

25 Tozer, F M On the Histological Diagnosis of Experimental Scurvy, *Biochem J* **12** 445, 1918

26 Cope, Z Fusion Lines of Bones, *J Anat* **55** 36-37, 1920-1921

Stevenson,²⁷ in his exhaustive survey of ossification in the collection of human skeletal material in the Western Reserve Museum, has focused considerable attention on them. These lines of fusion appear in the nineteenth and twentieth years, and may persist to extreme old age both in the longitudinal section and in the roentgenogram of the bone. Such lines of fusion are either thin, slightly sinuous lines of extremely dense bone, or narrow belts of cancellous tissue of a greater degree of compactness than the surrounding bones. In the undersized person with a history of severe illnesses in childhood or adolescence the lines may be wide and compact and associated with premature fusion and cessation of growth before the nineteenth and twentieth years. Such lines are more easily distinguished at the knee, ankle and shoulder and are rarely seen at the elbow or wrist.

G The General Distribution of Bony Striations—Bony striations resembling those described in Part I of this article have been seen repeatedly in routine examination of patients and in particular they have been observed in those adolescents who have suffered severe exanthemas in late childhood. They have been observed in conjunction with those cases presenting the so-called "peribronchial" fibrosis to a marked degree in the lower lobes of the lung. The lines have been seen in the case of adult chronic invalids who have been in indifferent health after severe illnesses in childhood and are frequently associated with irregularities of dentition, both as regards eruption of the teeth, suppression of the third molar, and those irregularities of the palate associated with the adenoid facies. In one specimen of a femur of a 6 months fetus in the Anatomical Museum of University College there is a well marked line 1 cm proximal to the epiphyseal line at the lower end of the femur.

Dr McKim Marriott of St. Louis presented me with figure 4, the roentgenogram of the tibia of a girl, aged 14 years, who suffered great privation in Russia for thirteen years. At present the girl is dwarfed and shows no lesion except large tonsils. She was breast fed, did not walk or talk until 3 years of age, and her bones were then said to have been "soft." Figure 4 shows no trace of adolescent rickets, but nine lines of dense bone are seen at the lower extremity of the tibia within a distance of 5 cm. These lines do not pass to the circumference of the bone and are shorter and more attenuated as the distance from the epiphysis increases. The tibia presents only a slight degree of forward bowing in the shaft. The patient had been diagnosed as a "rickety dwarf."

A closely allied phenomenon is seen in deciduous trees. In the first place, the rings of wood laid down during the vernal ascent and

27 Stevenson, P. H. Age Order of Epiphyseal Union in Man, *Am J Phys Anthropol* 7 53, 1924.

autumnal descent of the sap have distinct structural characteristics. In addition to this seasonal variation, marked examples of cessation of growth can be seen. A deciduous tree subjected to an unsuitable environment, such as excessive drought, during the early summer responds by a premature formation of cork across the base of the leaf stem and one half of the foliage may be prematurely shed. This protective mechanism decreases the area of functional transpiration, and the deposit of cork at the base of the leaf stem presents that pathologic cessation of growth that is normally seasonal in the deciduous tree, and normally adolescent in the coniferous tree.

H. Rickets and the Vienna Report—In a previous article²⁸ the clinical signs of early rickets employed by the Vienna School have been criticized. A few further remarks are necessary. The roentgenograms of the bones of a "normal" infant given by Wimberger²⁹ are not normal but show distinct bony striations at the upper and lower ends of the diaphysis of the tibia. These are evidence of periods of cessation of growth which may be due to any one or more of the causes that give rise to such lines. If on the various medical charts of the report the date of onset of an acute illness is marked it is obvious that the "line of dense ossification" may well be diagnosed as evidence of cessation of growth rather than as healing rickets. In charts 5 to 11, 14 to 17 and 19 and 21 an acute illness was present before healing rickets was diagnosed. In charts 22 to 27 there are several cases in which healing rickets was diagnosed roentgenographically by the line test within thirty days of acute influenza or bronchitis. A careful study of the medical charts and roentgenograms will show that bony striations occur quite distinct from the line of healing rickets. The roentgenograms are equivocal.

In a report of eighty-four selected cases examined histologically for evidence of rickets by Dalyell and Mackay, Wimberger²⁹ says that only twenty-eight were normal. Of the remainder, twenty-five showed rickets, three showed scurvy and twenty-eight showed syphilitic change, osteoporosis or other abnormal condition. Of the twenty-eight cases that were histologically diagnosed as rickets only ten were so diagnosed clinically before necropsy, and the two cases of proved scurvy, histologically diagnosed, were labelled as rickets before necropsy. This indicates that too much specificity cannot be credited to the "rickety rosary" and that every patient coming to necropsy, other than from sudden accidental death or acute poisoning in a healthy child, will tend to show abnormal features in the neighborhood of the epiphyses.

28 Harris, H. A. Some Problems of Bone Growth, *Proc. Roy. Soc. Med. (Sect. Electro-Therap.)* 17: 35-48 (Oct.) 1924.

29 Wimberger, H. A Study of Developing, Florid and Healing Rickets as Demonstrated by X-Ray Photography, *Studies of Rickets in Vienna 1919-1922*, London, 1923, p. 204, plate I.

PART III

THE GENESIS OF THE TRANSVERSE STRIATIONS IN BONE IN
RELATION TO VITAMINS AND TISSUE CULTURE

The wide distribution of bony striations leads to the suggestion that all such cases are manifestations of relative cessation of growth in length of the bone. The character of the striation is not so much influenced by the nature of the stimulus producing cessation of growth as by the duration of the stimulus. Roentgenographically and histologically the line of bony tissue will tend to be thin and compact or will consist of a band of several thin lines (embroidery effect) or of a heavy meshwork (lattice effect), according as the stimulus is acute and precise, or intermittent, or chronic and persistent. In an active patient or animal the remodelling of the bony trabeculae will be rapid, in an inactive patient or animal the remodelling may never occur. As a general rule, in man the bones at the elbow, shoulder and wrist, in accordance with greater use, will present rapid remodelling of the trabeculae and nonpersistence of the striations, at the hip, knee and ankle, especially if the patient is bedridden, the striations will tend to persist.

Bony striations are a normal feature of all animals at the time of cessation of the growth cartilages and register in bone the previous site of the epiphyseal cartilage as soon as the latter ceases to proliferate. Such striations tend to persist into extreme old age. They are veritable tombstones, marking the site of cell colonies that have passed away. Pathologically, bony striations are formed in the growing animal whenever there is cessation of growth at the epiphyseal cartilage. The density of the line tends to be proportional to the nociceptivity of the growth destroying stimulus. The persistence of the line in after life is determined by the functional use of the part. The stimulus to cessation of growth may be starvation, dehydration, an acute infection of the respiratory, urogenital or alimentary systems, or a deficiency disease such as scurvy. Experimentally, the lines can be produced in growing rachitic animals by the exhibition of cod liver oil, sunlight, ultraviolet rays, or restoration of the normal calcium-phosphorus ratio. Whenever such a line has been formed, its disappearance can be entirely or partly accomplished by functional use of the part.

Three processes are involved in normal bone formation at the epiphyseal line. Histologic examination shows, first, a zone of proliferative cartilage in which the cells exhibit the characteristic arrangement in columns or palisades, the number of cells in the normal column varying for the different animals, with a norm in the neighborhood of five. Second, there is the zone that displays calcification of the matrix and progressive degeneration of the cartilage cells. Third, there is

the zone in which osteoblasts are scattered over the trabeculae with capillary loops of the marrow blood vessels intervening. Each of these three zones is concerned particularly with one process. The first zone of proliferative cartilage is concerned purely and simply with proliferation. Adopting the terminology of Burrows,³⁰ it represents "a stagnant cell mass" deficient in vascular supply and is an area of minimum potential. Such a stagnant cell mass is comparable to a tumor, such as a tubercle, gumma, fibroid or cancer, in its metabolic processes, with maximum proliferation and minimum differentiation. This process of proliferation requires the substance or substances that Burrows has called "archusia," a water-soluble product that is closely related to the water-soluble growth promoting group of vitamins. The second zone, characterized by degeneration of cartilage cells and calcification of the matrix, is the area on which great light has been thrown by the experiment of Robison.³¹ By exposing one half of a longitudinally sectioned tibia to a watery extract of embryonic "whole bone," Robison has demonstrated that the latter contains an enzyme that produces effective calcification of the matrix of the growth cartilages in the tibia. The processes of calcification and degeneration taking place in the cartilage bear a close resemblance to the changes that take place in tumors, especially in tubercles, gummas and fibroids. The concomitant processes of calcification and degeneration are not only a feature of morbid anatomy but also of normal growth.

The third zone is the area of active osteogenesis. Those cartilage cells which are in proximity to the blood stream become polarized and undergo rapid differentiation with liberation of active osteoblasts. Burrows has ascribed the process of differentiation at the periphery of the stagnant cell mass to the presence of a blood borne substance termed "ergusia," which is fat-soluble and closely related to vitamin A. The process of liberation of osteoblasts from the degenerating cartilage cells is a rapid explosive amitotic process comparable to that seen in spore formation in fungi and bacteria. In addition to this older theory of Ranvier regarding the origin of the osteoblasts, the possibility of osteoblasts being formed from any primitive connective tissue cell, either from the periosteum or the reticulum of the bone marrow will not discredit the characteristic of this zone, i. e., rapid multiplication and differentiation of cells for the special function of osteogenesis.

Thus, the three zones are shown to be the seat of processes that have their counterpart in normal anatomy and in morbid anatomy. The

30 Burrows, M. T. Studies to Determine the Biological Significance of the Vitamins, *Proc Soc Exper Biol & Med* **12** 241-245, 1925. Burrows, M. T., and Johnston, C. G. The Action of Oils in the Production of Tumors, *Arch Int Med* **36** 293-332 (Sept.) 1925.

31 Robison, R. The Possible Significance of Hexophosphoric Esters in Ossification, *Biochem J* **17** 286-293, 1923.

three zones require, in order, a growth promoting vitamin, a calcifying enzyme, and a differentiating vitamin. The growth promoting vitamin of the proliferating cartilage closely resembles the water soluble archusia of Burrows. The differentiating vitamin of the bone area closely resembles the ergusia of Burrows.

In normal adolescence, the quantity of archusia is decreased and the stagnant cell mass of cartilage at the epiphysis ceases to proliferate. The cartilage has reached the limit of size beyond which it cannot live by imbibition of tissue juice, devoid of a definite blood supply. Calcification and degeneration take place therein under the action of the enzyme of Robison and, last, bone formation takes place under the action of ergusia. The process of bone formation is such that not only are the longitudinal trabeculae formed in true bone but cross bars of bone unite them one to the other to form a meshwork. In cases of marked athrepsia the meshwork is particularly well marked, especially as regards the transverse bars that connect the trabeculae. Their density and persistence tend to be inversely proportional to the amount of ensuing functional use of the part.

It may be asked what are the probable effects of an increase or decrease in the amount of archusia, enzyme and ergusia, respectively? An increase in the amount of archusia leads to increased proliferation of the cartilage cells and the trabeculae may increase from five cells deep to as many as twenty, i e., rapid proliferation without differentiation, as is seen in overactive normal growth and in clinical and experimental rickets. A decrease in the amount of archusia will reduce the cartilage columns to three or even one cell, as seen in cessation of growth from any cause whatsoever, whether normal or pathologic. Such cases are shown by Tozer²⁵ in the study of scurvy and by Hess, McCann and Pappenheimer²³ in rats fed on what they describe as a "fat-soluble A deficient diet." The composition, character and value of this diet have been questioned by McCollum. It is an "athreptic" diet rather than a "vitamin A deficient diet."

An increase in the amount of Robison's enzyme would lead to rapid calcification of the matrix and rapid degeneration of the cartilage cells. Such an increase is seen in those animals, e g., man, in which union of the epiphyses is concentrated into a short space of time and in which cessation of growth is rapidly brought about. Stevenson,²⁷ in his recent studies on epiphyseal union, has shown that cessation of growth of the long bones takes place almost entirely in the nineteenth year. On the other hand, the examination of a large number of skeletons of the rat and hedgehog has never produced a skeleton with complete epiphyseal union in all the long bones, i e., the period of epiphyseal union

is long drawn out, as described by Alden Dawson³² This period of union of the epiphyses may be related to the cycle of development of the gonads Robison's enzyme may be effective in controlling those disproportions of calcium and phosphorus which tend to produce rickets, for Park³³ has shown that the proportions of calcium and phosphorus are of more importance than the absolute quantities

If Robison's enzyme is deficient in quantity then the calcification and degeneration will be inadequate The calcification of the matrix may be uniformly deficient or it may be patchy Consequently, the degree of degeneration of the cartilage cells may be uniformly deficient or may be patchy In the so-called "florid rickets" of Wimberger,²⁹ the calcification is of the patchy type and is characterized in the roentgenograms by the feathery, fluffy or irregular margin that he so well portrays in this report If the calcification and degeneration are uniformly deficient, then the edge of the calcification zone is relatively straight, devoid of the feathery tufts, and is marked by its increased distance from the bony epiphysis This picture conforms closely to rickets of the "passive type" of Wimberger Histologically, the calcified zone displays the same characters as seen above If the calcification is patchy, then islands of uncalcified cartilage may be carried on into the shaft of the bone as is frequently seen in rickets of the florid type The trabeculae are irregular in arrangement and particularly is this so near the center of the bone If the calcification is uniform then the trabeculae are of uniform length, with poorly developed interruption of small blood vessels in them The epiphyseal line tends to be regular and there is no marked cupping or collapse of the line

Last, as regards the third zone, deficiency of the blood borne fat-soluble ergusia leads to failure of osteogenesis The degenerating cartilage cells, brought into contact with the capillary tufts, fail to produce active osteoblasts and sound bone The cells produced (whether from the chondroblasts or other connective tissue cells) resemble connective tissue cells in that they are somewhat flattened, the nuclei stain poorly, the protoplasm shows numerous basophilic granules, and fibrillar processes are marked Bone formation is defective, connective tissue formation is excessive and roentgenographically and histologically the picture is one of osteoporosis

The growth promoting factor necessary for the active proliferation of cartilage in the first zone is closely related to water-soluble vitamin B Many experimenters, especially Hess,²² reported failure to produce rickets on a diet deficient in vitamin A, and several, especially Osborne

32 Dawson, A B The Age Order of Epiphyseal Union in the Long Bones of the Albino Rat, *Anat Rec* **31** 1-18, 1925

33 Park, E A The Etiology of Rickets, *Physiol Rev* **3** 106-163 (Jan) 1923

and Mendel,³⁴ showed that the addition of orange juice to the diet provided not only the antineuritic vitamin B and the antiscorbutic vitamin C but also small quantities of fat-soluble A. Goldblatt³⁵ has shown that orange juice, as judged by biologic experiments, contains traces of fat-soluble vitamin A. In all these experiments the animals were on an athreptic diet and did not grow. The addition of orange juice afforded the necessary growth promoting vitamin B. The animals grew and then acquired rickets because of the deficiency in fat-soluble A. Interesting light has been shed on the growth promoting water-soluble archusia by my colleague, Wright³⁶. He has shown that the archusia can be separated from egg yolk by dialysis and that its activity on tissue cultures is ten times that of the nondialyzed egg yolk. Thus, although archusia and ergusia occur together in egg yolk, the water-soluble archusia can be separated from the fat soluble ergusia. The close relationship of the water-soluble growth promoting vitamin to water-soluble vitamin B and C, instead of to fat-soluble A, is thus explained. Fat-soluble A is not the growth promoting vitamin. Rachitic children are not deficient in growth promoting vitamin, athreptic children are. There is no justification for referring to fat-soluble A as growth promoting. The apparent contradictions of the experiments performed with a vitamin A deficient diet are clearly explained if this fact is grasped.

McCarrison,³⁷ in his classical account of beriberi has stressed the importance of the earlier manifestations of deficiency diseases as distinct from the lesions in the master tissues of the body, which are not so much signs of deficiency disease as signs of impending dissolution. The important signs of beriberi are (1) distaste for food, loss of appetite or depraved appetite, (2) gastro-intestinal derangements, indigestion, colitis and intestinal fluxes, (3) loss of weight, weakness and lack of vigor, (4) headache, anemia, tendency to edema and unhealthy skin and (5) subnormal temperature and vascular depression. Finally, the clinical picture may be completed by the later appearance of symptoms due to malnutrition of the nervous system, the master tissue of the body. Thus, cessation of growth precedes nervous phenomena and the latter are essentially terminal as they are in such conditions as pernicious anemia, pellagra, hematorporphyrinuria and saturnine encephalopathy. It cannot be too strongly urged that the signs of deficiency in vitamin B which are looked for in most biologic experiments are signs that are acquired late and precede death, long after cessation of growth has

34 Osborne and Mendel. *Proc Soc Exper Biol & Med* **19** 187-188, 1922

35 Goldblatt, H. A Study of the Relation of the Quantity of Fat-Soluble Organic Factor in the Diet to the Degree of Calcification of the Bones and the Development of Experimental Rickets in Rats, *Biochem J* **17** 298-326, 1923

36 Wright, G. P. Presence of a Growth Stimulating Substance in the Yolk of Incubated Hen's Eggs, *Proc Soc Exper Biol & Med* **23** 603-605, 1926

37 McCarrison, R. *Studies in Deficiency Disease* London, 1921, p 65

been established. The earlier signs enunciated by McCarrison are the real sign posts.

As regards rickets, the experiments of McCollum, Simmonds, Becker and Shipley³⁸ have led to the separation of the vitamin A of earlier observers into two elements. The one is a thermostable substance that is not destroyed by heating cod liver oil at 120 F. for twenty hours in excess of oxygen. This is the thermostable substance which is proved to be concerned with the calcification process and bears a close resemblance to the calcifying enzyme of Robison. It is usually referred to as vitamin X, or the true antirachitic factor. The other element is vitamin A proper, which is thermolabile, and is destroyed by heat and oxidation. This is the substance that is concerned with differentiation of cartilage cells to form osteoblasts, and it closely resembles the fat-soluble ergusia of Burrows. A deficiency of this substance leads to osteoporosis, sclerosis and disordered bone growth.

Any given case of rickets can be analyzed in terms of the three processes described: (1) proliferation of cartilage, (2) calcification and degeneration of cartilage, and (3) liberation of osteoblasts and bone formation. The roentgenographic and histologic pictures can be interpreted in such a way as to show which one or more of the processes are disordered. Paik,³⁹ in his analysis of the low calcium and low phosphorus forms of rickets, shows that the low calcium form is characterized by evidences of resorptive activity, and cells from the fixed tissues of the body lie scattered about in the immediate vicinity of the trabeculae. Cod liver oil never restores the finer structure of the bone to the normal. The trabeculae do not become completely calcified and the provisional zone of cartilage is not always completely calcified. The bone formation will be irregular, for an adequate supply of vitamin A proper will lead to liberation of osteoblasts and normal bone formation, but defective calcification and degeneration of the cartilage with insufficient vitamin A proper or ergusia will lead to formation of those cells which might be termed osteoidoblasts. Islets of uncalcified cartilage may be carried on into the shaft. The picture is "patchy."

On the other hand, the low phosphorus form of rickets presents cartilage which is more uniformly calcified, and subsequent bone formation will depend on an adequate supply of vitamin A proper or ergusia. The picture is less "patchy."

Is the low calcium type of rickets related to Wimberger's florid type, and is the low phosphorus type related to the passive type? As recently pointed out by Chisholm,³⁹ in Wimberger's florid type there is

38 McCollum, E. V., Simmonds, N., Becker, P. J., and Shipley, P. G. Studies in Experimental Rickets. XXI. An Experimental Demonstration of the Existence of a Vitamin Which Promotes Calcium Deposition, *J. Biol. Chem.* **53**: 292-312, 1922.

39 Chisholm, K. Rickets, *Brit. M. J.* **1**: 740-742, 1926.

a tendency on clinical examination to underestimate the amount of bone change, and in Wimberger's passive type there is a tendency, on roentgenographic examination, to underestimate the amount of bone change. In other words, the florid type is manifested particularly by obvious changes in the zone of calcification and degeneration, and the passive type is manifested by changes that are more marked in the zone of ossification. Seasonal tides of the blood phosphorus have been shown by Hess and Lundagen⁴⁰ and this seasonal tide, if dependent on the richness of absorption of ultraviolet energy, becomes an important factor in the passive type of rickets.

The pathology of bone disease has led to a series of names, and fetal bone disease, as reviewed by Ballantyne,⁴¹ has given rise to endless names. Vrolik's⁴² "osteogenesis imperfecta" is the only comprehensive name invented for all groups. It is submitted that all diseases of the skeleton, fetal and postnatal, can be analyzed and described in terms of the three processes of (1) cartilage proliferation, (2) calcification and degeneration, (3) osteogenesis. The pathology of bone can thus be interpreted in terms of disordered physiology. Such a classification has a valuable time element, for the fetal group of diseases are concerned principally with chondrodystrophy, the infantile group are concerned principally with defects of calcification, degeneration and osteogenesis, and the adult group are concerned almost exclusively with the osteogenesis involved in the remodelling and repair of adult bone in connection with absorptive phenomena and functional use.

Leg Weakness in Chicks—The recent studies of "leg weakness" in growing chicks by Pappenheimer and Dunn⁴³ afford an interesting example of the genesis of the changes occurring in this disease. Roentgenographic and histologic study of the legs are reported to show no rachitic changes, but the bone shows "an arrest of osteogenesis, osteoporosis, and fibromyxomatous transformation of the marrow." The administration of the antirachitic concentrate of the nonsaponifiable portion of cod liver oil did not prevent the onset of the lesion nor modify its character. However, the addition of whole cod liver oil prevented leg weakness and brought about normal bone structure. Thus, the disease is concerned only with the process of osteogenesis, and is due to deficiency of fat-soluble vitamin A proper (ergusia).

Burrows⁴⁴ pointed out that his experiments have shown that the ergusia in the developing chick reaches a minimum at the beginning and

40 Hess and Lundagen. Seasonal Tide of Blood Phosphate in Infants, *Proc Soc Exper Biol* **19** 380-382, 1922

41 Ballantyne. Antenatal Pathology, Edinburgh, 1904

42 Vrolik. *Tabulae ad Illustrandum Embryogenesis*, Tab XCI, Amsterdam, 1849

43 Pappenheimer, A. M., and Dunn, L. C. The Relation of Leg Weakness in Growing Chicks to Mammalian Rickets, *J Biol Chem* **66** 717-729, 1925

end of the period of incubation, with a maximum about the tenth day of incubation. Thus, at the end of the incubation period the conditions are favorable to the onset of that osteogenesis imperfecta that is due to the liberation of defective osteoblasts under the influence of insufficient *ergusia* or fat-soluble vitamin A proper. The curve for the variation in quantity of *archusia* is of the converse type with a maximum at the beginning and end of incubation and a minimum at about ten days. The chick of ten days corresponds to the human embryo of about the eighth week, differentiation has reached its maximum and henceforth the chick or embryo is concerned with growth rather than with differentiation. Organogeny is established.

The errors of growth of the first two months of human embryonic life are thus clearly differentiated from those of later life, and the conception of *archusia* and *ergusia* opens up a new basis for analyzing the causal factors in teratology. A new conception of the "time factor" is thus made possible in terms of the actual amounts of *archusia* or *ergusia*, substances that can be quantitatively assessed by their effect on tissue cultures under standard conditions of temperature, oxygen supply and rate of fluid flow. Figure 5 shows the extent to which the various processes of bone formation can be analyzed and shows the close connection between the interpretations thereof in the light of two methods of experiment, animal feeding and tissue culture. The morbid processes of bone growth can thus be interpreted in terms of disordered physiology.

Teeth and Membrane Bones—The same processes are involved in the development of the teeth and membrane bones of the skull and face. The teeth present problems in terms of those processes of growth, calcification and ossification which can be registered roentgenographically from the sixteenth week of embryonic life to adult age. The membrane bones, involving the suppression of the intermediate stage of chondrification and calcification are characterized by failure to ossify as seen in dysostosis cleidocranialis, or by imperfect osteogenesis, as seen in craniotabes. The victim of a severe illness in childhood tends to show permanent teeth that are crowded, with deficiency of calcification in the dentine and deficiency of enamel formation in the transverse striations of the enamel of the permanent teeth.

The processes of bony absorption present the same features. Poor osteogenesis not only signifies poor osteoblasts but also poor osteoclasts, and the processes of absorption of bone involved in the growth of the air sinuses are defective. Thus, the victim of a severe illness in childhood tends to show maldevelopment of the air sinuses, recessive chin, crowded teeth with transverse striations, and an infantile type of skull.

CONCLUSIONS

1 Transverse striations in the long bones of a nonrachitic child are described and the views of Hunter with regard to growth in length stand confirmed over a period of two years

2 Transverse striations are shown to be manifestations of cessation of growth. They occur normally in adolescence, they may occur with seasonal variations in the rate of growth, they occur in all cases of marked decrease in rate of growth from any form of acute illness or starvation. They occur as part of the healing process in rickets.

3 The skeletal processes are analyzed in terms of (1) the area of cartilage proliferation, (2) cartilage calcification and degeneration and (3) ossification proper. These three areas are related to (1) a water-soluble growth promoting vitamin or vitamins, (2) the enzyme of Robison, or vitamin X, and (3) the fat-soluble vitamin A proper.

4 These processes are discussed in terms of the archusia or growth promoting principle, and the eigusia or differentiating principle of Burrows, as enunciated for results obtained from cultures of normal and pathologic tissues.

5 A rational basis is suggested for the analysis of the processes involved in diseases of cartilage and bone, applicable to all ages.

6 The interpretations of the various "schools" concerning the agents and methods of healing rickets are considered and the fallacies of the "line test" are indicated. Cessation of growth is the important factor.

7 The term growth promoting as commonly applied to vitamin A is a misnomer. The growth promoting vitamins are water-soluble.

PRIMARY CARCINOMA OF THE THYMUS

REPORT OF A CASE¹

I I LEMANN, M D

AND

JOHN SMITH, M D

NEW ORLEANS

The rarity of primary carcinomas of the thymus is indicated by the fact that only three cases have been reported since the article of Rubaschow¹ in 1911. He had gathered from the literature reports of sixty-nine tumors of the thymus, fifty-two sarcomas, twelve carcinomas and five undetermined growths. A further search of the literature has revealed another carcinoma reported by Pollosson and Piery² in 1901 (apparently overlooked by Rubaschow), one by Honda and Taguchi³ in 1921, one by Symmers and Vance⁴ in 1921 and one by Jacobson⁵ in 1923. The case herewith reported is therefore the seventeenth primary carcinoma of the thymus recorded.

REPORT OF CASE

History—A. L. L., aged 58, a traveling salesman, came under observation, Feb 5, 1925. For three months he had had constant pain in the left hypochondrium and lumbar region. There had been constant pain in the right side for about two months. For two months heaviness in the epigastrium came on after eating or drinking, even of water. The appetite was poor, and he ate only soft food. The pains were so excruciating that he did not feel like eating. However, he had no nausea and no vomiting. He thought he had lost a little weight. He had no cough but expectorated a small piece of mucus in the morning. There was no shortness of breath, no palpitation. The past history was not particularly interesting. He could not recall any diseases of childhood nor had he been seriously ill during his adult life. Many years before he had had gonorrhea, which was followed by stricture, and he had been treated for "bladder trouble" three years before and had gone for prostatic massages from time to time. The family history is of significance only in that two sisters had died of carcinoma.

Physical Examination—The physical examination showed a poorly nourished, small man, 5 feet 3 inches tall, weighing 118¾ pounds (53.8 Kg). He was evidently in great pain and walked into the office holding his side and back,

¹ From the department of medicine, Tulane University of Louisiana School of Medicine, and from the pathologic service, Touro Infirmary, New Orleans.

1 Rubaschow. Eine boesartige Thymusgeschwulst, Virchows Arch f path Anat **206** 141-157, 1911.

2 Pollosson and Piery. Un cas d'epithelioma primitif du thymus, tumeur polykystique congenitale du cou chez un enfant, epithelioma infiltré, Province med **15** 1-4, 1901.

3 Honda, I., and Taguchi, K. Ueber primare boesartige Geschwulste des Thymus, Gann **15** 57-59 (Dec.) 1921, abstr., J. A. M. A **78** 772 (March 11) 1922.

4 Symmers, D., and Vance, B. M. Epithelioma of Thymic Origin, Arch Int Med **26** 239 (Sept.) 1921.

5 Jacobson, V. C. Primary Carcinoma of Thymus, Arch Int Med **31** 847-856 (June) 1923.

bending somewhat forward The skin was dark olive (normal) There was no adenopathy The mucous membranes were normal The tongue was slightly coated and the teeth were poor The tonsils were negative, the lungs were normal, the heart was of normal size The dulness measured 8 cm from the midline in the fifth intercostal space, 2 cm to the right There was no retro-sternal dulness The heart rate was 100 The blood pressure was 120 systolic, 70 diastolic There was no murmur and no irregularity There was marked peripheral arteriosclerosis The abdomen was slightly enteroptotic The liver was felt two fingerbreadths below the costal margin The spleen was not felt The pupils were equal, regular, symmetrical, and reacted to light and accommodation The knee jerks were normal The dorsolumbar spine was very stiff The urine showed hyaline casts and a few leukocytes The red blood cells showed no abnormality The hemoglobin was 95 per cent The Wassermann reaction was negative

Treatment and Course—The back was strapped, and this afforded great relief After ten days it was necessary to remove the strapping because of skin irritation At this time a skiagraph of the spine was taken and the radiologist reported that there was evidence of hypertrophic arthritis of the spine A plaster jacket was applied by Dr E S Hatch, March 2 This, however, afforded the patient little relief and it was necessary to give him acetylsalicylic acid and codeine He walked around for nearly a month wearing the cast, complaining always of excruciating pain April 3, he was readmitted for observation because there was marked edema of the right leg and foot and some of the left leg Because of this the cast was removed, April 7 April 8, the following note was made "There has been a constant grunting and complaining since his admission While he says he cannot sleep, very often sleep has been induced by hypodermics of sterile water or by sugar capsules At others times phenobarbital has been used The edema of the lower extremities has continued, much more marked on the right than on the left Last evening the cast was removed by Dr Hatch because of the patient's constant complaint of its pressure This morning he declares himself free of pain but complains of weakness of the whole body, especially of the back" The querulousness still continued The edema gradually disappeared after the removal of the cast Apparently the edema had been due to pressure on the femoral veins The patient continued to complain constantly, "I can't get a comfortable position My body has no strength I have pain in the back and right knee" April 17, the report was, "There is no doubt that the patient has grown considerably weaker He has complained constantly of this weakness and pain in the right knee He is made to stand up for the first time since the cast was removed and there is now evident in the left interscapular space a tumor about the size of an orange from about the level of the seventh to that of the ninth or tenth dorsal vertebrae To the outer and upper side of this tumor there is exquisite tenderness, over the swelling itself, dulness and diminished respiratory sounds Just beyond it toward the scapular side the respiratory sounds are exaggerated" Fluoroscopic examination showed a large pulsating mass in the chest This was interpreted by the roentgenologist as an aneurysm It was thought, therefore, that his pains might be explained on the basis of an erosion of the spine The patient continued to lose strength and weight and to complain constantly of excruciating pain in the back The temperature, which had been normal in February and March, began in April to show frequent elevations to the neighborhood of 100 F This rise later became a daily occurrence April 12, the hemoglobin had fallen to 65 per cent and the red blood count was 4,080,000 There was a slight anisocytosis The leukocyte count was 10,750, neutrophils, 81, small lymphocytes, 18, and eosinophils, 1 April 20, the red cells had fallen to 3,565,000, the hemoglobin remained 65 per cent, the leukocyte count was 13,000 The neutrophils totaled 79, the small lymphocytes, 10, the eosinophils, 3, and the basophils, 1 The urine continued to show hyaline and an occasional granular cast but no other abnormality April 28, the report read, "In the last few days a second protuberance has developed in the back This second protuberance is on the right side

opposite the tenth and eleventh ribs. It is exquisitely painful. Edema of both feet and both legs is present, more marked on the right." It was apparent that an aneurysm could not proceed as rapidly as this and that there could be but one explanation of the appearance of the masses in the back, namely, that they were metastases. It was believed, therefore, that the mass seen in the chest was not an aneurysm but a neoplasm. A skiagram made at this time was reported as showing a large neoplasm involving the entire mediastinum. The patient continued to grow weaker and more emaciated. The tumors grew larger, more superficial and more fluctuating. The skin became edematous. They were sensitive but not extremely so. There was no pulsation and no thrill over them. June 27, the upper one on the left extended from about the level of the sixth or seventh vertebra to that of the ninth dorsal vertebra. The lower one on the right extended from about the ninth or tenth dorsal vertebra to the first or second lumbar. The patient continued to have a slight daily rise of temperature—from 99.5 to 100 F. He



Fig 1—Retropleural metastasis, under low power, Hassall's corpuscle shown above and to the left of the center, in the dark in the upper center staining is a collection of small round cells, large polyhedral cells in chains and sheets form the bulk of the picture, in the center is a lymph space

suffered a great deal from pain in the back and a burning sensation all around the middle of the body. It was necessary to give him morphine in increasing doses up to 15 gram daily. At times he expectorated bloody mucus. The weakness grew progressively greater so that he slept most of the time. He came to a point where he ate practically nothing. For the last three or four days of his life he had retention of the urine and it was necessary to catheterize him. He was conscious practically to the end. About one-half hour before death, he was given a gruel, he choked, vomited and was prostrated from exertion. From this he passed into the final unconsciousness.

Necropsy—The body was that of a fairly well developed but poorly nourished white man, measuring about 5 feet 3 inches and weighing about 95 pounds (43.1 Kg). The skin was sallow, rather soft and pliable. Postmortem rigidity and

lividity were absent. The pupils were equal and measured about 7 mm. On the posterior surface of the thorax was a semifluctuant mass on the right side involving the ninth, tenth and eleventh ribs immediately anterior to their attachments to the vertebrae. On the left side was a similar mass about 6 cm in width by 10 cm in length involving the seventh, eighth and ninth ribs. An attempt at aspiration with forcible suction obtained a very small amount of thick caseous necrotic material. Superficial lymph nodes were palpable but not enlarged. The abdomen was flat.

Pleural Cavity. The sternum was found firmly adherent to an underlying mass extending from the episternal notch to the level of the fifth rib. Both pleural cavities were filled with an amber fluid. There were a few adhesions in both right and left apices. The mediastinum was occupied by a large tumor mass measuring 12 cm in length by 10 cm in breadth which extended from the sternal

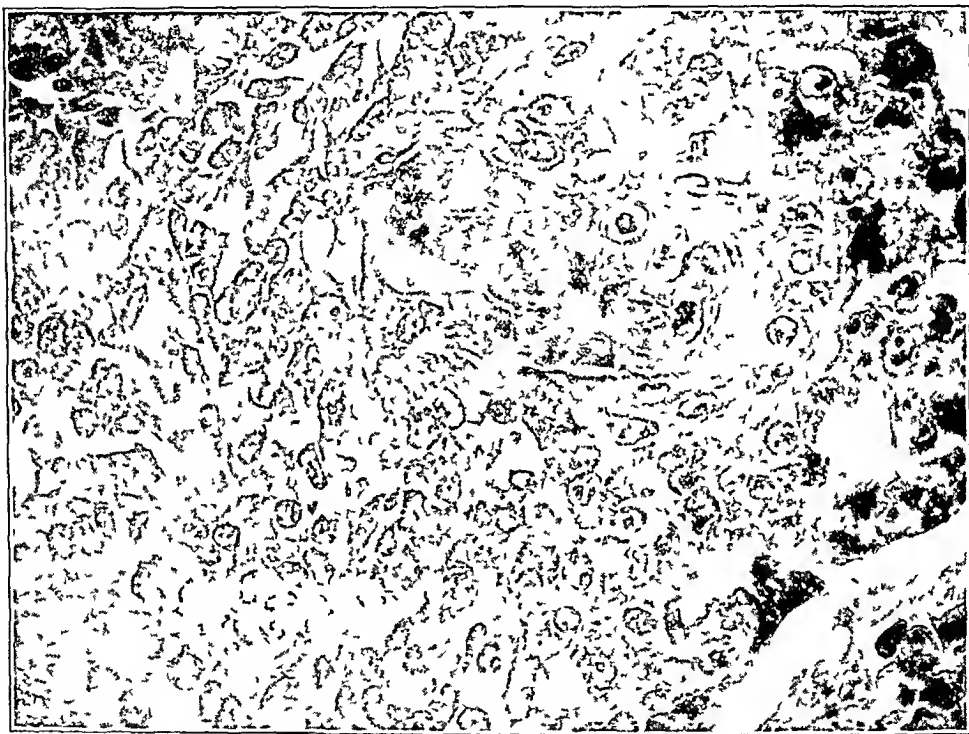


Fig 2—Part of the field of figure 1, showing detail of Hassal's corpuscle, under high power

notch and pressed on the base of the heart, forcing that organ downward. This mass was adherent to the parietal pleura on both sides and to the pericardium beneath. It was firm in consistency for the most part although here and there were found fluctuating areas which were filled with clear amber fluid. It was growing around the great vessels of the heart. On section it showed considerable resistance to the knife and presented a dirty yellow cut surface. It appeared to be made up largely of dense connective tissue with here and there groups of cells less firm in consistency, some of which showed dirty yellow necrotic areas. After the removal of the lungs an oval semifluctuant mass was found in the right pleural cavity corresponding to the mass described on the external surface. This mass was covered by pleura and on sectioning was found to be a secondary neoplasm that had destroyed the ninth, tenth and eleventh ribs from the angle of their attachment to the spine. The laminae of the corresponding vertebrae were destroyed and replaced by the new growth, with the result that there was a communication with the spinal canal. On the left side was a similar mass involving the seventh, eighth, ninth and tenth ribs.

Pericardial Cavity The pericardial cavity was pressed on by the tumor mass above described and its anterior wall was thickened by this tumor mass. The inner surface was smooth. On both sides of the pericardium, particularly on the right, there was a mass of dilated veins measuring 2 by 3 cm. The heart was relatively small and its outer surface showed no pathologic changes. It was dark brownish red.

Lungs The right lung at its apex showed a few areas of healed tuberculosis and on its upper surface were tags of adhesions. It was adherent also in its middle and upper lobes to the growth in the mediastinum and also to a tumor mass in the posterior chest wall. It was rather doughy in consistency and with the exception of a small amount of edema was negative. The left lung showed a similar condition to the right. The peribronchial lymph nodes were somewhat enlarged but on section showed no macroscopic evidence of neoplasm.

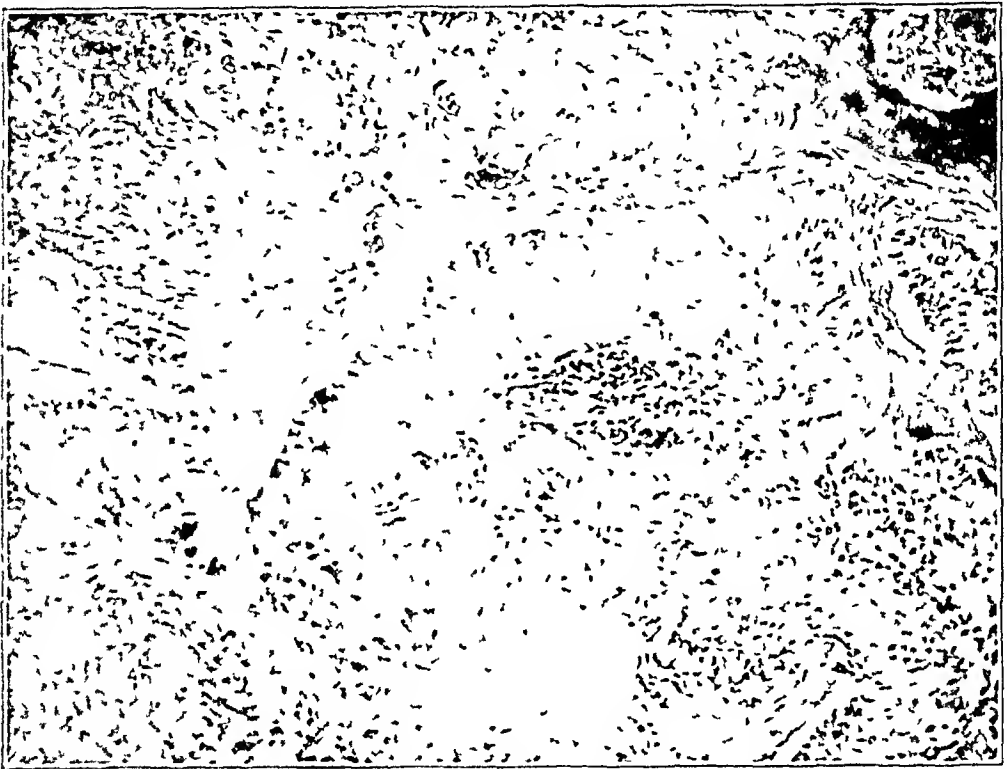


Fig. 3—Metastasis eroding the vertebrae under low power, bone is shown in the upper right corner.

Abdominal Cavity This was free from fluid or evidences of an inflammatory reaction. The omentum covered the intestines and was adherent by old adhesions to the cecum and adjacent wall. The liver was pushed downward, its lower border being on a level with the umbilicus. The lesser abdominal cavity was negative.

Spleen The spleen measured 10 by 6 cm and weighed about 120 Gm. It was firm in consistency and was adherent by old adhesions to the surrounding tissue. On sectioning it offered increased resistance to the knife and the cut surface showed an increased amount of connective tissue. The pulp was rather firm, maroon, and did not readily come off to the knife. The malpighian corpuscles were not prominent.

Liver The liver measured 25 by 18 by 10 cm. It was dark brown, somewhat mottled in appearance and rather smooth for the most part, although there were noted several secondary new growths that produced irregularity in contour. One was situated on its anterior surface just below the dome in the midline of the right lobe. Another was found on the inferior surface of the left lobe. On

section the liver presented a nutmeg appearance. A number of small pinkish gray areas were present throughout the structure in addition to the masses visible on the outer surface. These masses were rather circumscribed, more or less spherical in outline, and in addition to their pinkish gray color showed many foci of necrosis.

Pancreas. This was normal.

Suprarenals. The suprarenals were normal.

Kidneys. Both kidneys presented the same picture. They were buried in a mass of firm perirenal tissue and were quite firm in consistency. When the capsule was peeled off, it was adherent and left an outer surface that was rough and irregular presenting the picture of persistent fetal lobulations. On section the kidneys offered increased resistance to the knife and showed some thinning of the cortex and an increase generally of connective tissue. The parenchyma was dirty yellow.

Prostate. The prostate was normal.

The anatomic diagnosis was primary neoplasm of the thymus, secondary neoplasm of the liver, lungs and bones, chronic interstitial nephritis, chronic splenitis, passive congestion of the liver, and pleural effusion.

The microscopic diagnosis was neoplasm of the mediastinum, that is, carcinoma of the thymus gland characterized by the presence of Hassal's corpuscles, in the lungs, bronchopneumonia, chronic pleuritis and anthracosis, secondary neoplasm (thymus), in the bone, secondary neoplasm ((thymus), in the liver, fatty degeneration, passive congestion, and secondary neoplasm (thymus), in the kidneys, chronic interstitial nephritis and cloudy swelling, in the spleen, fibrosis, pigmentation and passive congestion. The pancreas was normal. The intestines showed degeneration of the mucosa and localized areas of congestion.

COMMENT

Ewing⁶ has remarked, "No group of tumors has more successfully resisted attempts at interpretation than those of the thymus." Even a cursory review of the literature reveals the confusion that has existed. Some authors have evaded definite classification and have been satisfied to state the evident malignant nature of the growth. Ewing has made two main groups: (1) lymphosarcoma or thymoma, arising probably chiefly from the reticulum cells and probably lymphocytes, and (2) carcinoma arising from the reticulum cells. He calls attention to the varying nomenclature employed by different writers and to the existence of apparent transitional forms connecting the two types. It is significant, he remarks, that carcinomas have been recorded almost entirely by the French, while practically all the German reports have been of sarcomas. Some of the authors have described as carcinomas tumors that have many of the features designated by others as those of sarcoma. The lymphosarcomas are often encapsulated tumors occupying the mediastinum. They may, however, present extensions by continuity and may metastasize to other viscera or to the bone. The microscopic picture varies greatly but most of these tumors (lymphosarcomas) fall into one of three groups:

⁶ Ewing, J. Report of Three Cases of Thymoma, Surg Gynec Obst 22 461 (April) 1916.

A Tumors showing many small round cells and plasma cells and some large polyhedral cells, suggestive of the granuloma cells of Hodgkin's disease

B Tumors showing a large number of polyhedral cells with comparatively few of the small round cells (These tumors have been classified by some of the French as carcinomas)

C Tumors in which the large polyhedral cells tend to form sheaths about the blood vessels, suggesting, therefore, the diagnosis of perithelioma

When these tumors show metastases the large polyhedral cells are the ones most commonly seen in the secondary growth. At times they tend to form structures simulating Hassal's corpuscles. The gross picture of carcinomas of the thymus is similar to that found in the harder of the lymphosarcomas but metastases are more common. There is also usually more dense connective tissue stroma with islands of isolated cells. There are areas of necrosis with a tendency to cyst formations. The flat or polyhedral cells are arranged in cords, sheets and islands. There is a rather marked tendency to form Hassal's corpuscles and at times structures resembling glandular acini. As a rule, the small round cells are relatively few and the connective tissue stroma is dense. The large polymorphonuclear cells observed in these tumors are of two types: (1) cells with a single nucleus and pale staining acidophilic cytoplasm often showing vacuolization, and (2) cells with a deeper staining, more opaque acidophilic staining cytoplasm with multiple vesicular nuclei. Concentric layers of cells with flattened or elongated outlines and nuclei form structures resembling Hassal's corpuscles.

The neoplasm in our case was designated a carcinoma primary in the thymus because the primary growth was in the anterior mediastinum, appeared to spring from the thymus, did not show direct continuity with contiguous structures and presented the following features:

Gross—(a) A rather firm tumor occupying the anterior mediastinum and pushing the heart downward and showing some fluctuant cystlike areas.

(b) A cut surface, of dirty yellow color, presenting a dense connective tissue stroma that separated islands of cells. There were many yellow necrotic areas.

(c) Secondary growths on the posterior chest walls to the right and left of the vertebral column. These growths showed no direct continuity with the primary tumor. Metastases to the liver and the lungs which were rather well circumscribed and cellular in nature.

Microscopic—(a) In the primary tumor were sheets and cords of cells, mostly large polyhedral cells, showing many structures resembling

Hassal's corpuscles These cell groups were well surrounded by a dense connective tissue stroma There were few small round cells in the primary growth Fluctuating structures were apparently due in part to degeneration and in part to secretion Tendency to form acini was rather marked in the primary growth

(b) The picture in the secondary growths was similar to that seen in the primary growth but there were fewer small round cells and a less dense connective tissue stroma Hassal's corpuscles were present here in moderate numbers In the secondary growths on the chest wall the tendency to form acinus-like structures was marked In the liver growth little of this tendency was noted

The present case is of interest not merely as a rarity but as pointing certain definite clinical lessons It was apparently impossible to make a diagnosis of intrathoracic neoplasm at the time that he first came under observation He had at that time no symptoms pointing to intrathoracic disease and yet we must believe that the growth had already metastasized into the lumbar vertebrae The excruciating pain of which he had been complaining for three months can be explained only in this manner The roentgenograms taken of the spine at that time showed no indication of this metastasis but merely a hypertrophic arthritis which undoubtedly coexisted Nor would one have been apt later on to make a diagnosis of the thoracic growth on the basis of physical signs even when we were quite sure from other evidence that the disease did exist It was only at the very last of the illness that he expectorated bloody mucus There was at no time evidence of pressure on the trachea nor on the bronchi nor on the vena cava and other large vessels, nor was there displacement of the heart All this seems remarkable in view of the size and position of the neoplasm as discovered at necropsy The belief that the mass seen fluoroscopically was an aneurysm lasted but a few days It would have been extraordinary to see an erosion by an aneurysm advance so rapidly When, however, the second fluctuating mass appeared an erosion of this character could no longer be accepted The parallelism between Jacobson's case and ours is most striking In his case, too, the presenting symptom was that of pain and stiffness in the lower part of the back A plaster jacket was later necessary The general course of his case was very much like that of the case reported here The necropsy revealed a thymic growth with metastases into the lungs and into the vertebrae The primary growth differed from ours in being comparably small

SUMMARY

In the case of primary carcinoma of the thymus with metastases into the lungs, the liver and the vertebrae reported here, the presenting symptom was pain in the back The diagnosis of malignant intrathoracic

disease was made possible only by the appearance of evident metastases in the back and the discovery by roentgen ray of a shadow in the thorax. The intrathoracic growth gave rise to no local signs or symptoms. It is suggested that the possibility of thymus neoplasm be borne in mind when there is roentgenographic evidence of abnormality in the mediastinum. The possibility of this diagnosis is strengthened when metastases are found.

THE SPECTROPHOTOMETRIC ANALYSIS OF THE COLOR OF THE SKIN

AND THE OBSERVATIONS BY THIS METHOD IN NORMAL AND
IN PATHOLOGIC SUBJECTS *

CHARLES SHEARD, PH D

AND

GEORGE E BROWN, MD

ROCHESTER, MINN

As Rowntree and Brown¹ have stated in a recent article, there is a pressing need in clinical medicine for a method of measuring and recording the color of the skin. A diversity of terms and descriptive expressions exists in clinical literature in the varied attempts to state the color of the skin and its changes during the progress of the treatment of the patients under observation. For example, various clinicians have recorded the color in polycythemia as being "red," "brick red," "congestive red," "reddish cyanosis" and even "cyanotic." Our knowledge of color and color vision is fundamentally inexact and as a result the language of color, while it may be beautiful, lacks precision. For there are myriads of shades of red from the faintest pink to the darkest red, and yet they are all to be classified as being reds. The terms ordinarily used to describe color do not connote the same conceptions. And, again, it is well nigh impossible for any two pairs of physical eyes and sets of mental receptor organs to see the same "thing" or the same attributes of the "thing," whatever this may be. Furthermore, pigments and spectral colors are vastly different. The spectral colors of white light, such as sunlight, are pure colors, can be measured in intensity and purity and so on, and are, therefore, readily standardized. For instance, spectral yellow of a given wave length (say 590 millimicrons, or sodium yellow) is always the same yellow and can be exactly reproduced.

METHODS OF COLOR ANALYSIS

Two possible methods of analysis of the color of the skin are available. First, a comparison with color plaques, such as has been developed by Rowntree and Brown¹ in their universal skin tintometer of nine separate color scales which can be subjected to analysis by the Munsell²

* From the Section on Physics and the Division of Medicine, Mayo Clinic and the Mayo Foundation

1 Rowntree, L. G., and Brown, G. E. A Tintometer for the Analysis of the Color of the Skin, *Am J M Sc* **170** 341-348 (Sept.) 1925

2 Munsell, A. A Color Notation, ed 6, Baltimore, Munsell Color Company, 1923

system of color measurement, and, second, a spectrophotometric analysis of the color of the skin. Tintometric or colorimetric methods of estimating and recording color are doubtless of value in the practice of medicine. Such systems of classification as applied to color are of some aid in the diagnosis and in the course of the treatment of diseases in which appreciable color changes occur in the skin, as in jaundice, cyanosis, polycythemia vera, anemia, Addison's disease and hemochromatosis. However, such methods do not in any wise analyze the spectral light reflected by the skin and therefore cannot record in terms of the three attributes of color, brilliance, hue and saturation.

It is a well known fact in physiologic optics that white light can be spectrally made out of certain quantities of red, green and blue of limited wave length values or, again, out of certain quantities of orange, green and blue of limited wave length values, according to the color tables of Maxwell³ and others⁴. Hence, the expression "white light," in and of itself, states nothing about the components and the amounts thereof which go to make up the white light. And again, the definition of Addison's disease states that "it is a disease characterized by a bronzelike pigmentation of the skin"⁵. The expression "bronzelike" is very inexact, since nearly all of us have bronzelike coloration of the skin but this varies considerably in the quantity and distribution of the pigment, as will be shown later in the results recorded in this article. For a normal blonde, a normal brunette, a negro and a person suffering from Addison's disease differ from one another only in the amount of pigmentation, which is in large part melanin. Ordinarily, the degree of pigmentation is to be roughly thought of as a smoke screen (in some persons very slight and in others very dense) laid down between solar radiation, on the one side, and the blood in the peripheral capillaries on the other side of the dividing medium, the epidermis.

The three attributes of color are relative luminosity (brilliance), dominant wave length (hue) and purity (saturation). The percentage brightness of a color defines how much of the total amount of standard white light (sunlight or its equivalent) which falls on it any color is capable of reflecting (or transmitting). By the hue or dominant wave length is meant that attribute of the color which permits it to be classed as reddish, yellowish, greenish or bluish. Percentage of purity or

3 Maxwell, J. C. On the Theory of Compound Colors and the Relations of the Colors of the Spectrum, *Scientific Papers* 1 410-444

4 Sheard, Charles. *Physiologic Optics, Being an Essay Contributed to the American Encyclopedia of Ophthalmology*, Chicago, Cleveland Press, 1918, vol. 13, pp. 9720-10214

5 Dorland, W. A. N. *The American Illustrated Medical Dictionary*, ed. 12, Philadelphia, W. B. Saunders Company, 1923

saturation determines the degree of hue. Thus, the percentage of purity defines how red or how yellow, and so forth, a color is.⁶

Our complexions and the colors of our skins are dependent on a variety of causes. According to Lundsgaard and Van Slyke, the main factor that contributes to the production of cyanosis is the absolute amount of hemoglobin and the erythrocytes present in the peripheral vessels. This is subject to a group of modifying factors: (1) the area of exposure of the capillary blood, which depends on the number of open capillaries for each unit of surface area and the area of the exposed portion of the loops,⁷ (2) the thickness and pigment content of the epidermis, (3) the color of the blood plasma, either in the blood or in the tissues, (4) the color effect of the visible venules, which is related to their position with reference to the heart level,⁸ and (5) the variation in the oxygen unsaturation. The same factors hold true in a large

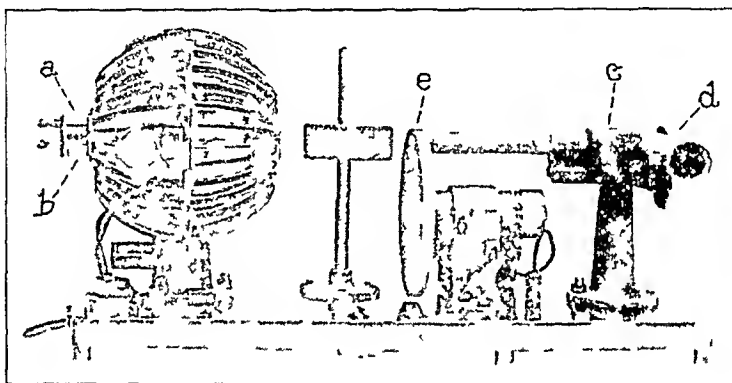


Fig 1—The spectrophotometer, or color analyzer

degree for color of the skin in general. Normal blondes and brunettes, for instance, differ only in the amounts of pigmentation. It is said "That the pigmentation of the skin bears some relation to health is well recognized. Tanned individuals are generally healthy. But whether the reaction is a direct or indirect one is unknown."⁹ We believe, however, that the condition of tan per se, which is due to the deposit of pigment, is not necessarily such an indication of health, because of the fact that the blood (by reason of the reflection of light from the blood in the capillaries at the surface of the skin) contributes its quota to the composite color of the skin as seen by the eye.

6 Report of Committee on Colorimetry, L. T. Troland, Chairman. *J. Optical Soc. Amer.* **6**: 527-596, 1922.

7 Brown, G. E., and Sheard, Charles. Measurements on the Skin Capillaries in Cases of Polycythemia Vera and the Role of These Capillaries in the Production of Erythrosis, *J. Clin. Investigation* **2**: 423-434 (June) 1926.

8 Goldschmidt, S., and Light, A. B. Cyanosis Unrelated to Oxygen Unsaturation, Produced by Increased Venous Pressure, *Am. J. Physiol.* **73**: 173-192 (June) 1925.

9 Mathews, A. P. *Physiological Chemistry*, ed. 4, New York, William Wood & Co., 1925, p. 711.

The eye is a poor instrument for analyzing or resolving the constituents of color. Spectrophotometric analysis of the light reflected by the skin and the subsequent further analysis of these data into red, green and violet excitation color values and relative luminosity values of the noonday sun as a standard, furnish the only strictly scientific means of obtaining information concerning the rôle played chiefly by pigment and blood in the color of the skin. So far as we know, no work has been done previously on this subject by such methods.

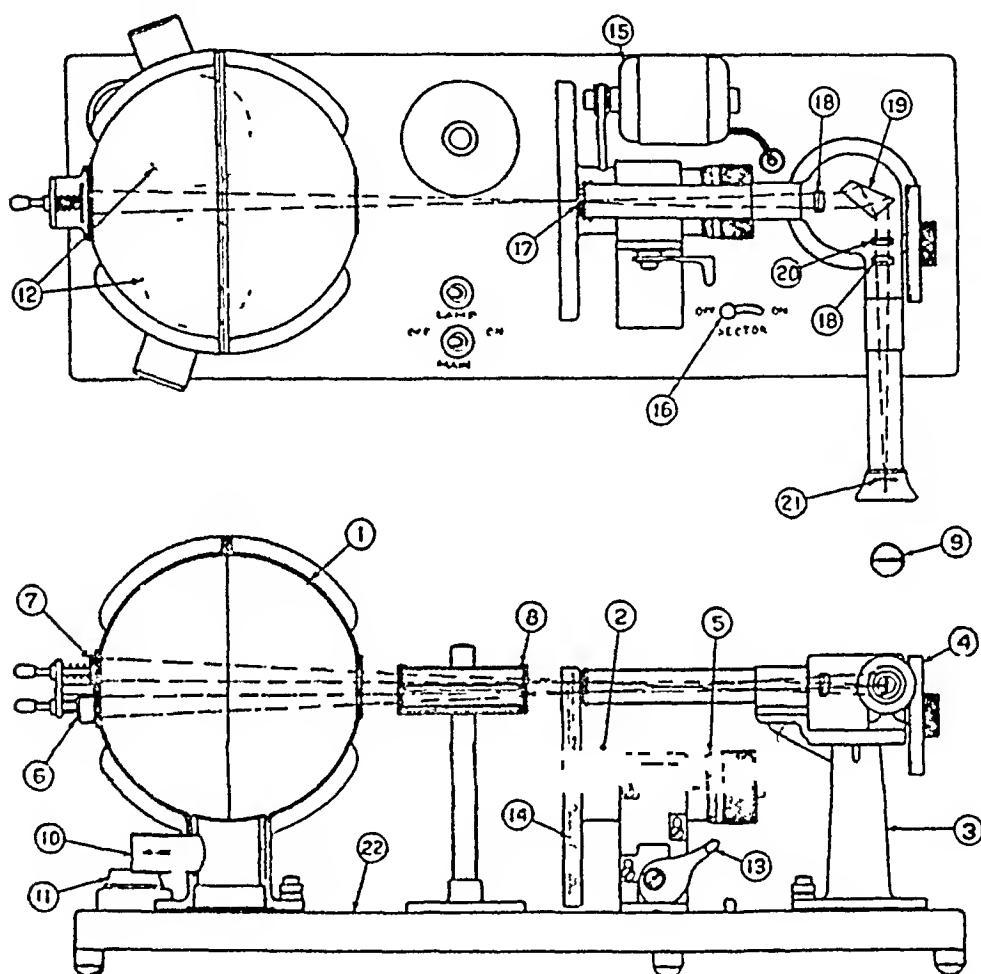


Fig. 2—Cross-section diagrams showing the working parts of the spectrophotometer, of which the following are noted: (1) spherical light source, (2) photometer, (3) spectrometer, (4) wave length scale, (5) photometer scale, (6) holder for standard sample, (7) holder for reflection samples, (9) field of view through the eye slit, (14) sector disks, (17) entrance slit, (19) dispersion prism, and (20) biprism.

SPECTROPHOTOMETRIC METHODS AND PROCEDURES

The spectrophotometer used in these investigations was one brought out recently by Keuffel¹⁰ and Esser and referred to in the literature as a "color analyzer." Figure 1 is a reproduction of a photograph of the

¹⁰ Keuffel, Carl. A Direct Reading Spectrophotometer, *J. Optical Soc. Amer.* **11** 403-410, 1925.

instrument Figure 2 is a cross sectional diagram showing the working parts of the machine and their arrangement as to the spectrometric and photometric operations The instrument consists essentially of a lamp house carrying two magnesium blocks, *a* and *b* (fig 1), cut from the same block, which are placed at the rear, these blocks serve as sources of light for transmissions through receptacles containing various liquids which may be introduced into the paths of light In these experiments, however, we are dealing with percentages of reflection rather than transmission The magnesium block *b* (fig 1) is therefore allowed to remain in place and the block *a* is removed and in its stead is placed the object (such as a finger, or the back of the hand) which is to be examined spectrophotometrically as regards its reflecting powers The two beams of light reflected by the block *b* and the hand (placed at *a*) enter the spectrometer *c* (fig 1) The spectrometer proper does not differ in fundamental principles from the ordinary constant deviation type of instrument except for the addition of a biprism, which is placed in front of the telescopic lens system, and an observing (exit) slit in the eyepiece Throughout the series of observations which are being reported in this article, the exit and entrance slits were kept at constant or fixed values, following the initial adjustment of the entrance slit to give 100 per cent transmission from the two magnesium blocks throughout the whole spectrum

The method of getting the data shown in figures 3 to 6 is as follows White light from two 400-watt stereopticon bulbs in the lamp house, after reflection from the block *b* and the fingers or portion of the hand placed at *a*, is admitted to the spectrometer The spectrometer, *c* (fig 1), is set at any desired wave length by means of a calibrated wheel, *d* (fig 1) As an illustration, with a setting at 590 millimicrons (which is close to the sodium yellow of the spectrum) the observer, on looking through the exit or eye slit, sees two semicircular colored areas in juxtaposition, with the dividing line horizontal Both halves of the circle will have the same hue (yellow) but not necessarily the same brightness or saturation value The adjustment for the equality of brightness, or a match, is then made by varying the size of the sector opening in the rotating sector, *e* (fig 1), placed in front of the spectrometer, *c* (fig 1), until the two halves of the field are equally illuminated The percentage reflection of light from the fingers (or hand) for any given wave length is read directly from a calibrated drumhead This drumhead is mechanically connected to the sectorized disks in such a manner as to permit of the rapid tuning of it by hand, thus providing a quick way of varying the relative proportions of open and closed sectors

The data on spectrophotometric reflection from portions of the body other than the fingers, such as the back of the hand or the palm

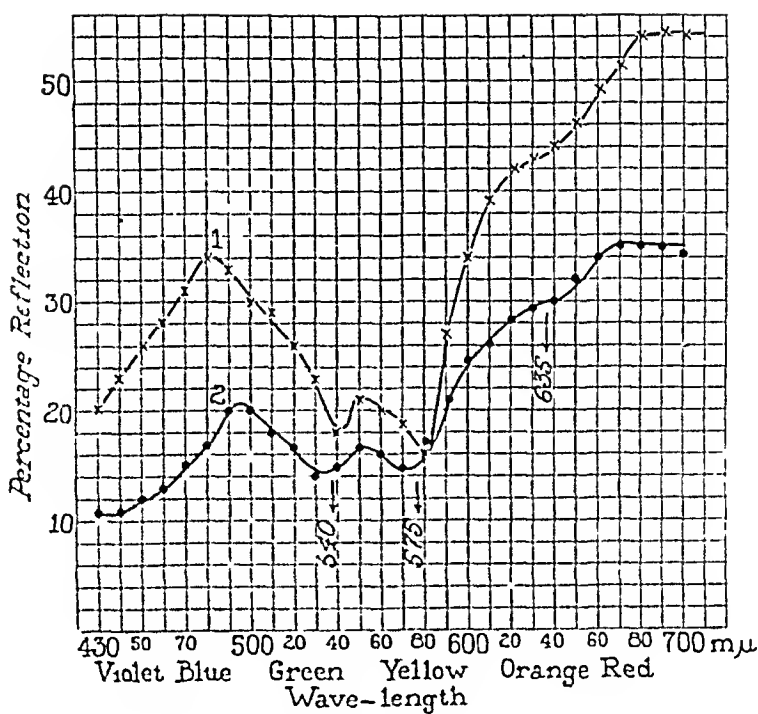


Fig 3—Spectrophotometric reflection curves curve 1, a normal blond, curve 2, a case of Addison's disease The absorption bands at 540, 575 and 635 millimicrons (or thereabouts) in these curves as well as in those of figures 4 to 6 should be noted The middle and ring fingers were used for obtaining spectrophotometric reflection curves in all conditions, both normal and abnormal, which are presented and discussed in this article

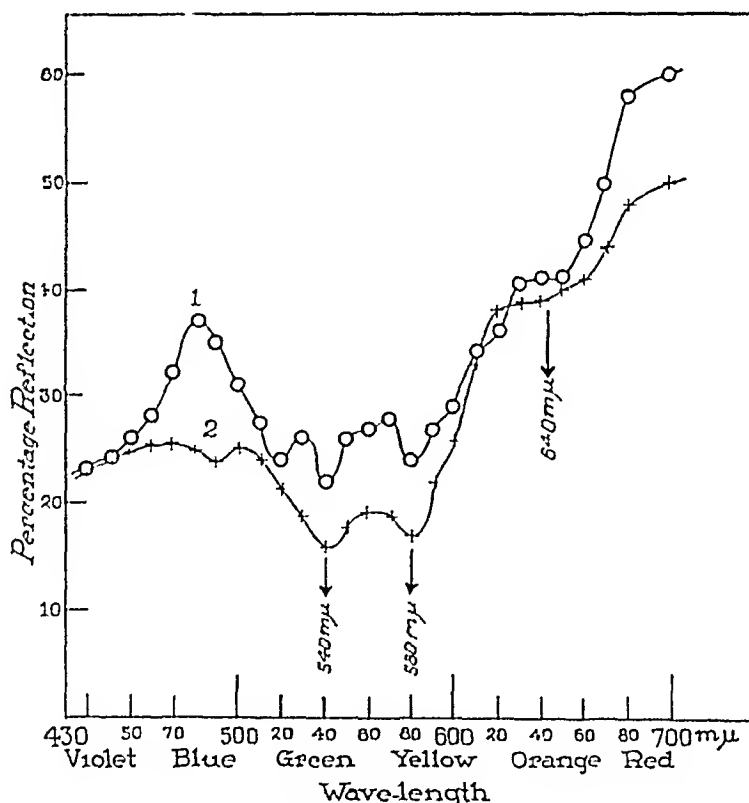


Fig 4—Spectrophotometric reflection curves in a case of polycythemia vera curve 2, before treatment with phenylhydrazine, and curve 1, three weeks after treatment was instituted

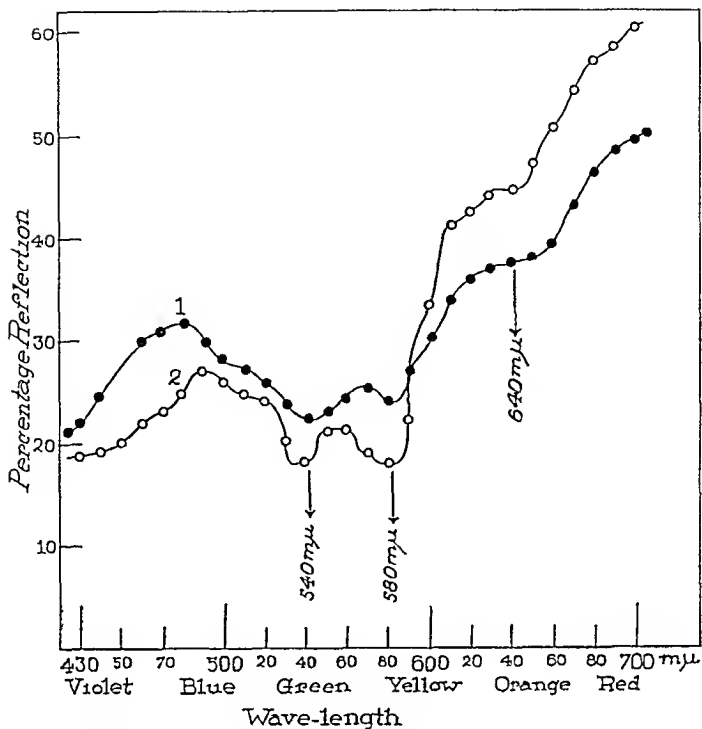


Fig 5—Spectrophotometric reflection curves in a case of polycythemia vera curve 2, before treatment with phenylhydrazine and curve 1, one month after the commencement of the treatment with phenylhydrazine

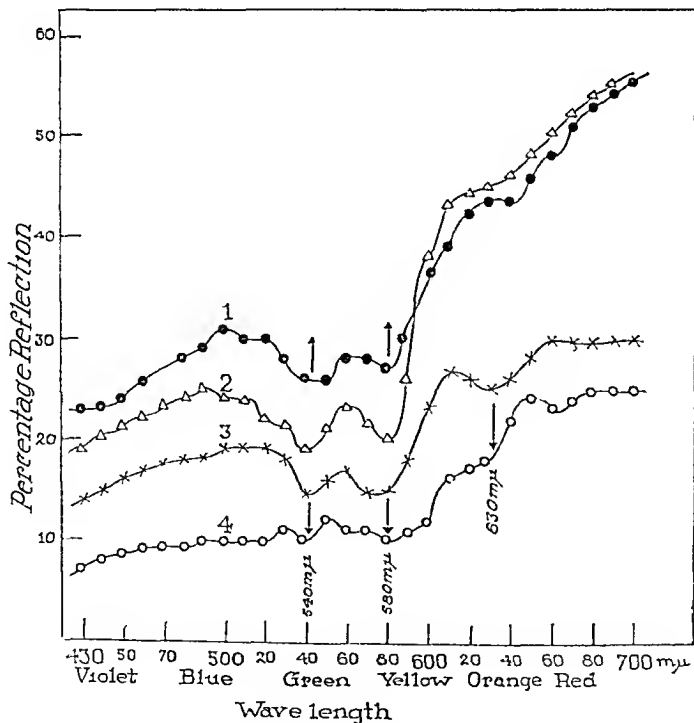


Fig 6—Spectrophotometric reflection curves curve 1, normal female brunette, curve 2, normal male brunette, curve 3, a case of scleroderma, and curve 4, a normal mulatto

of the hand, may be obtained with this instrument by a slight modification that we have introduced to take the place of the plate holding the blocks *a* and *b* (fig 1) We have substituted a concavoconvex metal screen with its concave side turned away from the lamp house proper A block of plaster-of-paris covered with magnesium oxide paint serves as the standard *b* (fig 1), and a portion of the face arm or body may be placed opposite the opening *a*

SPECTROPHOTOMETRIC REFLECTION CURVES IN CERTAIN NORMAL AND PATHOLOGIC CONDITIONS

Figures 3 to 6 give selected spectrophotometric reflection curves The legends accompanying these figures give the explanatory data In every instance the reflection curves were obtained from the middle and ring fingers of the left hand In figure 6 are plotted percentage reflection data for a normal blond (curve 1), a normal brunette (curve 2),

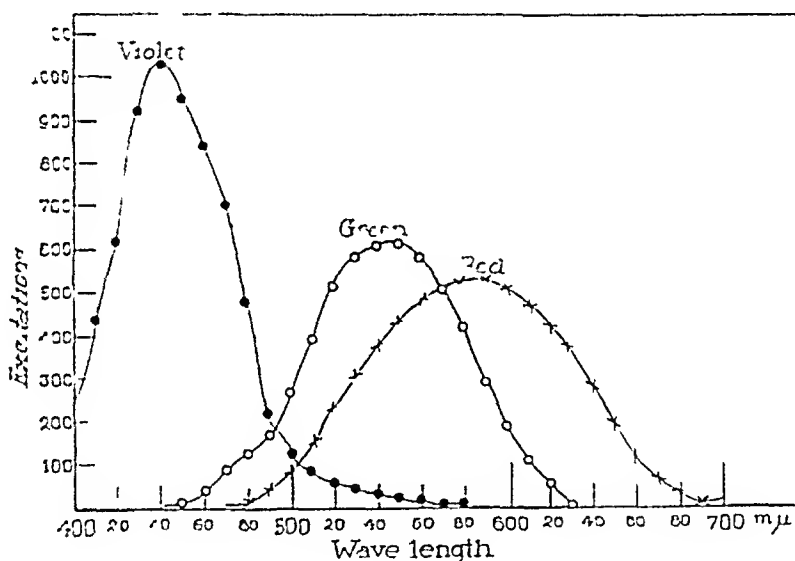


Fig 7—Elementary color excitations for different wave lengths

a negro (curve 4), and a person who had scleroderma (curve 3) An experienced eye might be able to take such a group of curves and to draw the correct conclusion that the only difference in these cases was in the amount of pigment present In all the curves of these figures there are indications of three absorption regions or spectral bands of lower percentages of reflection from the surface of the skin one in the red at approximately 630 to 640 millimicrons, due without doubt to hematin in the tissue cells, and two bands in the yellow-green region, 570 to 580 millimicrons and 530 to 540 millimicrons, which are due to the oxyhemoglobin absorption of light by the blood

Figures 4 and 5 present the spectrophotometric reflection curves from the fingers of patients suffering from polycythemia vera In each figure curve 2 represents the results before treatment with phenyl-

hydrazine, while curve 1 gives the spectrophotometric data after treatment. In both instances it can be seen that the percentage reflection is considerably increased in the region 450 to 580 millimicrons (blue to yellow) after treatment with phenylhydrazine

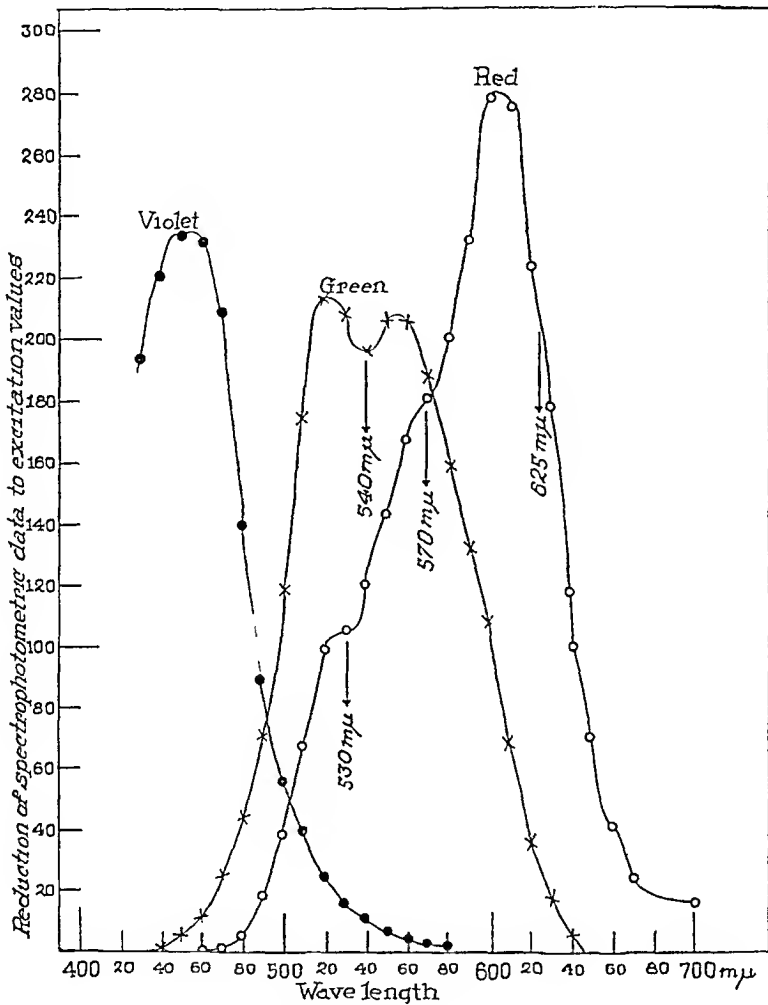


Fig 8—Analysis of the spectrophotometric reflection data from a normal blond (fig 3, curve 1) into the three primary color excitation curves

ANALYSIS OF SPECTROPHOTOMETRIC DATA INTO COLOR EXCITATION VALUES

Probably the most fundamental of all the psychologic data relating to color are the three color excitation curves, which represent the laws of three color mixture. Extant data on these relationships are due to Maxwell,³ Abney¹¹ and König and Dieterici¹². The results of the

11 Abney, W de W. *Researches in Color Vision and the Trichromatic Theory*, London, Longmans, Green & Co., 1913

12 König, A., and Dieterici, C. *Die Grundempfindungen in normalen und abnormalen Farbensystemen und ihre Intensitätsverteilung im Spektrum*, *Ztschr f Psychol u Physiol d Sinnesorg* 4 241-347 1892

latest investigations on this matter, reduced to an equal energy spectrum and referred to average noon sunlight, are plotted in figure 7

Spectrophotometric data are generally given in the form of curves of spectral transmission or reflection. Such curves require combination with a certain energy distribution (representative of the particular

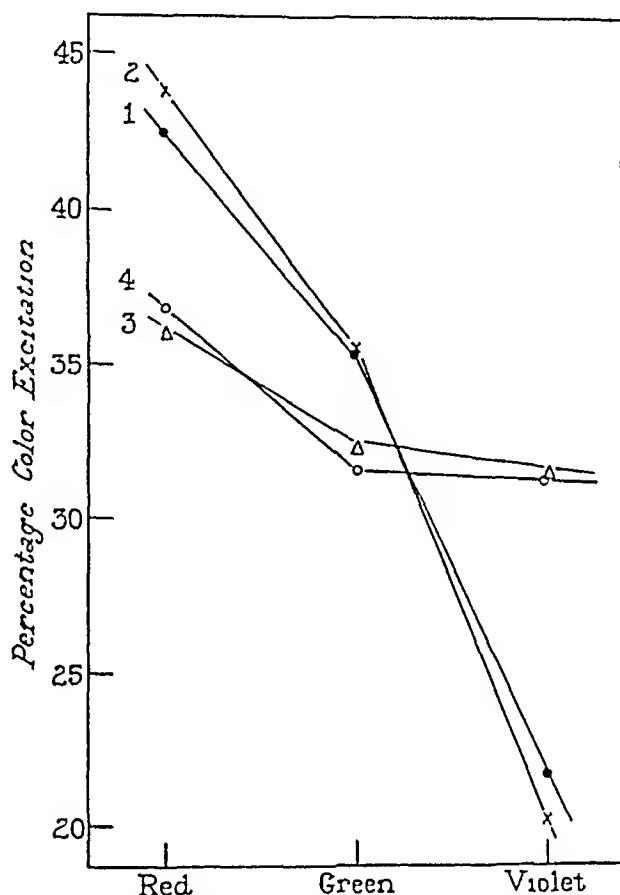


Fig 9—Percentage color excitation values as determined from the summation of the data obtained from the elementary color excitation curves: curve 1, normal blond, curve 2, normal brunette, curves 3 and 4, cases of polycythemia vera

source by which the object is viewed) in order that they shall become determinative of a definite color. The process of reducing any given set of spectrophotometric specifications to excitation values is therefore as follows: (1) Multiply each of the ordinates of the transmission or reflection curve by the corresponding ordinate of the energy distribution curve of the source, (2) multiply each of the ordinates of the resulting curve by the corresponding ordinate of each of the color excitation functions as shown in figure 7, this being a separate operation for each of the three excitations and yielding three separate curves which represent the respective excitation values for each wave length of the given stimulus, (3) determine separately the areas of the three curves thus found, (4) reduce the three areal values thus obtained to percentage

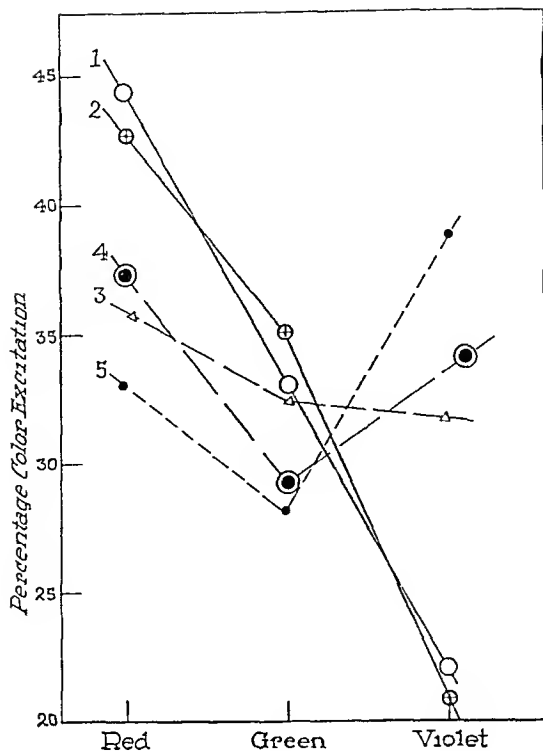


Fig 10—Percentage color excitation values curve 1, normal blond, curve 2, normal brunette, curve 3, a case of polycythemia vera before treatment with phenylhydrazine, curve 4, the same case three weeks after treatment with phenylhydrazine was instituted, and curve 5, a case of Raynaud's disease during the stage of cyanosis

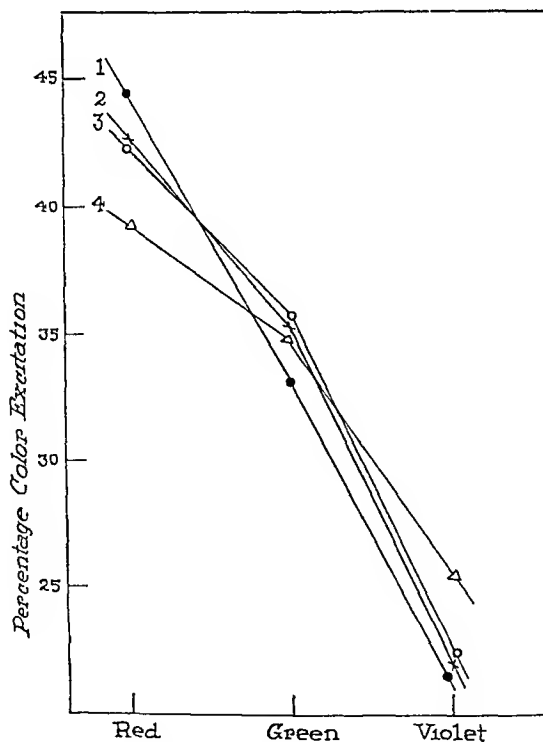


Fig 11—Percentage color excitation values curve 1, normal brunette, curve 2, a case of Addison's disease, curve 3, a normal negro, and curve 4, a case of scleroderma

form, so that then determined ratio remains unchanged but then sum becomes equal to 100. The color excitation values can then be expressed by means of two numbers, representing the red and violet excitation percentages, that for the green being obtainable by subtracting the sum of these two values from 100. Very complete details on these points are given in the report of the committee on colorimetry.⁶

Figure 8 contains the red, green and violet excitation curves for the spectrophotometric data given in curve 1 of figure 3, a case of a young normal blond. These excitation curves show the presence of spectral bands at 625, 570 and 530 to 540 millimicrons, respectively, as is evidenced also in figures 3 to 6. The conversion of the spectrophotometric curves into color excitation values (as outlined in the preceding paragraph) is much simplified and rendered more rapid by the use of a special slide rule prepared by Keuffel and Esser for this purpose.

We have followed the foregoing procedures in their applications to the curves of figures 3 to 6. In figures 9 to 11 are plotted the relationships existing between the fundamental color excitations (red, green and violet) and the percentage color excitations for normal blonds, normal brunettes, normal mulattoes and those affected with polycythemia vera, Addison's disease, Raynaud's disease and scleroderma. The data on the summated values for red, green and violet, as well as their percentages, are to be found in tables 1 and 2. In a general way the results of figures 9 to 11 show very conclusively that the relationship between percentage color excitation and wave length of color (red, green and violet) is approximately a linear one in normal persons in whom there are no abnormalities in quantity, quality or distribution of blood in the peripheral vessels and in whom the degree of pigmentation varies from slight to dense degrees. In cases of polycythemia vera, both before and after treatment with phenylhydrazine, and Raynaud's disease in which there are abnormalities in the quantity, quality and distribution of the blood, we find that the analysis of the color of the skin into fundamental excitation color values shows marked reductions in red and green and marked increases in violet when compared with normal skin, which is either slightly or highly pigmented.

In addition to these data regarding the summated values and percentages of red, green and violet in the white light reflected from the skin, there is also a dominant wave length (hue) and a degree of purity or saturation. A dominant wave length and purity chart are reproduced in figure 12. Using the color triangle and taking the percentages of red and violet for the various curves of figures 3 to 6, we are able to find the dominant wave lengths (or hues), as well as the degrees of purity and relative luminosities, which are recorded in table 2. Figure 13 gives a résumé of the dominant wave lengths in various normal and pathologic conditions that we have investigated. It will be noted that

the dominant wave length is yellow (from 595 to 575 millimicrons) in cases of normals (blond, brunette and negro), Addison's disease and scleroderma. The dominant wave length in polycythemia vera is red (610 to 650 millimicrons) before treatment with phenylhydrazine but

TABLE 1—*Color Excitation Values for Red, Green and Violet Obtained from the Spectrophotometric Data on the Skin of Normal Persons and in Certain Diseases*

Name	Figure	Curve	Clinical Classification	Total Red	Total Green	Total Violet	Remarks
J	9 3	1 1	Normal blond	2,600	2,186	1,340	Very fair complexion
P	10 6	2 2	Normal brunette	2,075	1,550	1,022	Average brunette
R	11	3	Normal negro	854	726	450	Average mulatto
M	3 9	2 2	Addison's disease	1,412	1,151	650	Advanced stage
L	11 6	4 3	Scleroderma	1,322	1,181	865	
T	10	5	Raynaud's disease	1,332	1,157	1,497	Cyanotic stage
H	9 4	3 All	Polycythemia vera	1,570 1,970	1,425 1,790	1,388 1,566	Before treatment with phenylhydrazine After treatment with phenylhydrazine
W	9	4	Polycythemia vera	1,264 1,330	1,127 1,140	1,200 1,130	Hand 30 cm above heart level Hand 30 cm below heart level

TABLE 2—*Percentages of Color Excitation Values, Purity and Relative Luminosity, and Values of the Dominant Wave Length in the Skin of Normal Persons and in Certain Diseases*

Name	Figure	Curve	Clinical Classification	Red, per Cent	Green, per Cent	Violet, per Cent	Dominant Wave Length, Milli-microns	Purity, per Cent	Relative Luminosity, per Cent
J	9 3	1 1	Normal blond	42.4	35.7	21.9	587	43	34.8
P	10 6	2 2	Normal brunette	44.5	33.5	22.0	585	40	27.1
R	11	3	Normal negro	42.1	35.7	22.2	585	45	17.3
M	3 9	2 2	Addison's disease	43.9	35.7	20.4	580	50	19.4
L	11 6	4 3	Scleroderma	39.2	35.1	25.7	583	28	18.6
T	10	5	Raynaud's disease	33.4	28.0	38.6	527	25	17.4
H	9 4	3 All	Polycythemia vera	35.8 37.1	32.5 29.4	31.7 33.5	605 497	10 20	20.3 25.3
W	9	4	Polycythemia vera	35.2 36.9	31.3 31.6	33.4 31.5	497 640	5 10	17.9 18.0

it becomes greenish (497 to 510 millimicrons) after treatment with phenylhydrazine. This is on account of the high serum bilirubin and temporary jaundice created by reason of the large amount of hemoglobin broken down with the liberation of the pigments.

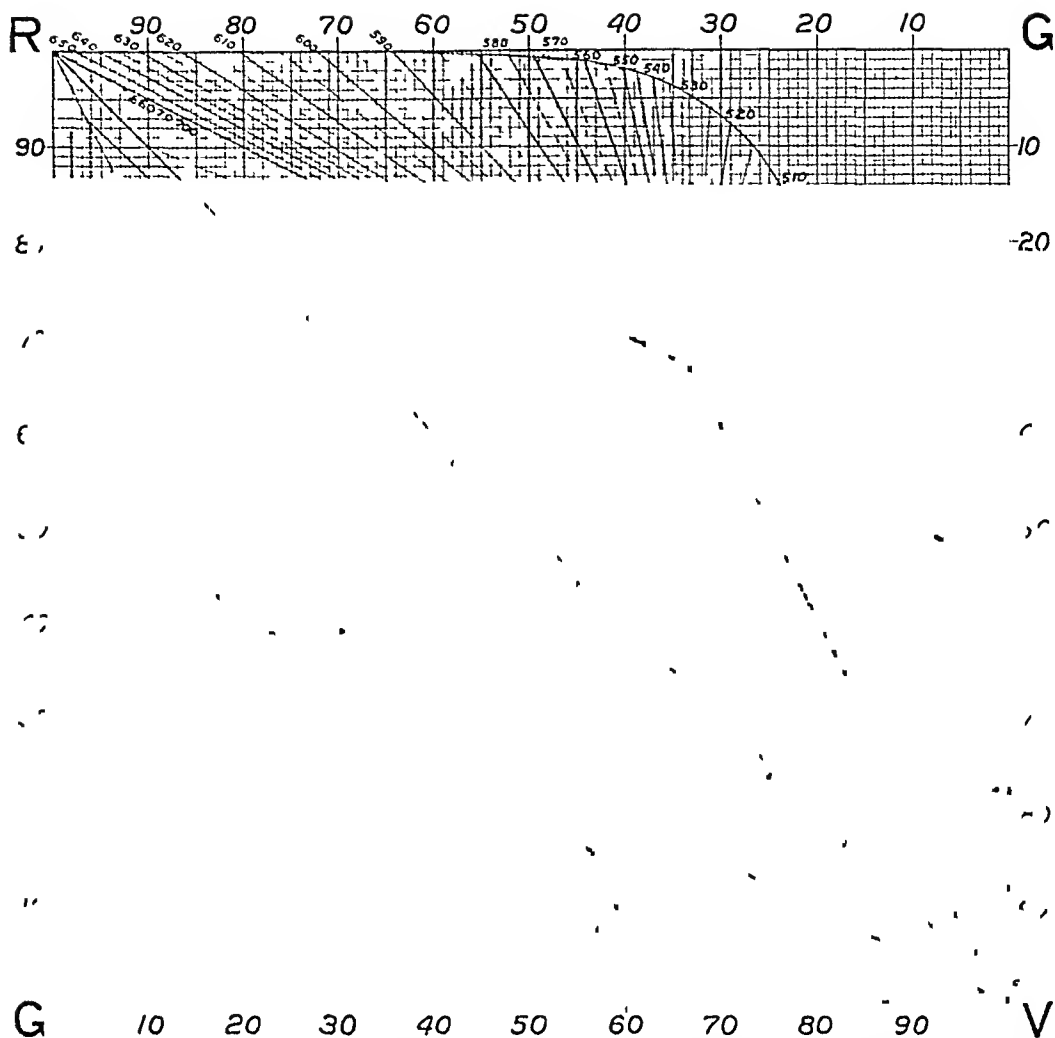


Fig 12—Dominant wave length and purity charts from which the hue and the degree of saturation may be obtained by the use of data from the percentage color excitation calculations

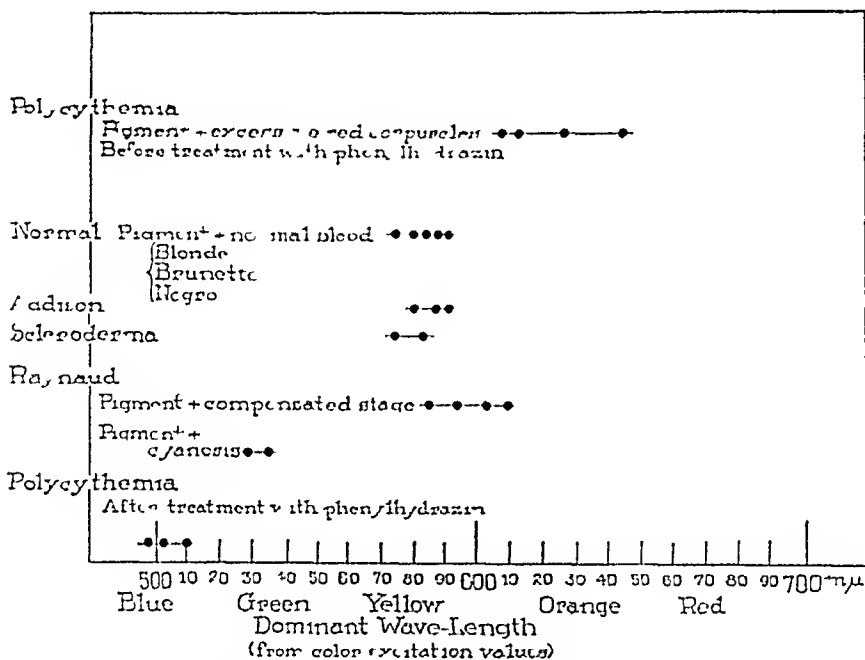


Fig 13—Relationships between the dominant wave lengths and various normal and pathologic conditions

Tables 1 and 2 contain a full résumé of the spectrophotometric data and the analysis into excitation color curves, dominant wave length, percentage of purity and percentage of relative luminosity

This method is being used or will be applied (1) to determine quantitatively the melanin present in both normal and pathologic conditions, (2) to standardize or furnish a biologic rather than a physical unit for dosages of ultraviolet or superficial roentgen-ray treatments in terms of the changes produced in the color of the skin, (3) to coordinate the degree of pigmentation and changes in superficial distribution of blood with other physiologic effects or changes such as occur in rachitis, for example, and (4) to estimate the degree and character of the changes in the color of the skin before and after treatment in cases of Addison's disease, polycythemia, anemia, jaundice, hemachiomatosis and other pathologic conditions in which there are departures from the normal in the color of the skin

CONCLUSIONS

1 The spectrophotometric method of analysis of skin color furnishes the basis for a relatively simple but bloodless method of depicting certain characteristics of the blood at the peripheral portions of the body

2 The spectrophotometric curves show the presence (or absence in certain cases) of (*a*) hematin, (*b*) reduced hemoglobin, (*c*) oxyhemoglobin, and possibly (*d*) methemoglobin in peripheral or superficial tissues and blood

3 It is probable that the spectrophotometric data as obtained from the skin by reflection methods may be of value in determining certain physicochemical characteristics of the blood

4 By spectrophotometric reflection curves and their subsequent analysis into fundamental red, green and violet excitation values, it is possible to differentiate between variations in skin color due to (*a*) pigment content and (*b*) the amount, distribution or quality of the peripheral blood supply

5 Spectral analysis shows that there is close agreement in the values of the dominant wave length, purity and percentages of red, green and violet in normal blonds, brunettes and mulattoes and in such pathologic conditions as Addison's disease. The dominant wave length is practically 585 millimicrons (nearly sodium yellow) in all instances

6 In cases of polycythemia vera, Raynaud's disease, during the stage of rubor, and allied conditions, there are marked departures from the normal condition in the values of the dominant wave lengths, purity and percentages of red, green and violet. In these diseases, in

which there are generally marked disturbances in the quantity, quality and distribution of blood, the dominant wave length is in the red (605 to 640 millimicrons in our observations)

7 Cyanosis is noticeable in various diseases. Spectrophotometric determinations and analyses in terms of monochromatic radiation show that the summated violet values are too high in comparison to similar summated values of the violet in normal subjects, and that there is a marked reduction in the summated values of the reds and greens in these diseases as compared with normal persons

CORRECTION

In the article by Drs Fahr and Swanson, "The Quantities of Serum Albumin, Globulin and Fibrinogen in the Blood Plasma in Acute and Chronic Nephropathies" (*Arch Int Med* 38 510 [Oct] 1926) the authors desire to substitute "standard deviation" for "coefficient of deviation" in Table I and also in the sixteenth line of reading matter on page 512

Book Reviews

NERVOUS AND MENTAL DISORDERS FROM BIRTH THROUGH ADOLESCENCE By
B SACHS, M D, and LOUIS HAUSMAN, M D Pp 861 Price, \$10 New
York Paul B Hoeber, 1926

Although based on a previous text (*Nervous Diseases of Children*, by B Sachs, M D), this volume is enlarged and rewritten to constitute a new and comprehensive work of 861 pages with more than 100 illustrations. The format is pleasing and the bibliography recent.

The structure and function of the central nervous system are briefly considered and methods of examination outlined in the opening chapters. Meningitis and epidemic encephalitis are well described, especially the pathology and possible etiology of the latter, although one might wish in a work of this sort for a discussion of behavior disorders following encephalitis, in view of their rather frequent occurrence nowadays. Infantile cerebral palsies are thoroughly discussed, especially as to pathogenesis—aside from some recent work on the occurrence and early diagnosis and treatment of meningeal hemorrhage in the new-born infant.

Neurosyphilis in the young is so rare, the authors feel that it merits comparatively little space, juvenile paralysis being described in small type. On the other hand, amaurotic family idiocy, though even more rare, is covered at considerable length, in which, however, the authors show entirely pardonable preference for the Tay-Sachs disease. The chapter on the progressive muscular atrophies is especially good, it is a clear and complete discussion with an eight page bibliography. In connection with multiple sclerosis the latest work on pathology is reviewed at length, especially that of Hassin. The description of the striatal syndromes is brief. Brain tumors and lesions of the peripheral nerves are fully reviewed, and epilepsy, though briefly considered, is related to the more recent literature, including such therapeutic efforts as Peterman's ketogenic diet and Joseph Miller's advocacy of protein desensitization.

The account of hyperthyroidism, while detailed, fails to describe the condition as it occurs in children. The reviewer, with other readers, no doubt, has not seen hyperthyroidism in a child and would like to be informed wherein, if at all, the symptoms differ from those in an adult, if surgical intervention is indicated as in older patients, and like points. A similar criticism might be offered in connection with a few other topics, since in a text of this character one looks especially for a picture of the immature organism's reaction to deficiency, degeneration and disease.

The section dealing with the development and training of the normal child is notable for an attack on psychoanalysis, summed up in the statements, "There is not a scintilla of scientific evidence in any part of this psychological doctrine. It is a speculation of the rankest sort." The authors state that to their knowledge many adolescents have been harmed by psychoanalysis, and for this reason they are impelled to denounce its practice. Dementia praecox, manic depressive and defective mental development are all adequately treated, the first exceptionally well.

Altogether, this is an excellent treatise, which many general practitioners, pediatricians and others will doubtless find useful.

A BIPOLAR THEORY OF LIVING PROCESSES By GEORGE W CRILE Edited by
AMY F ROLAND Cloth Price, \$5 Pp 405, with 62 illustrations New
York The Macmillan Company, 1926

The volume, according to the author, represents an attempt to present certain conclusions that are based on researches which have been in progress continuously from 1898 to the present time, and which were commenced to determine

the causes of fatigue, exhaustion and death. The researches followed four lines of study, the first three of which, circulation and respiration, blood chemistry and cytologic studies, gave no clue to the mechanism, the failure of which leads to fatigue, exhaustion and death. The fourth line of study, which the author terms biophysical studies, and of which the material of the book is composed, explains satisfactorily (to the author) the solution of the riddle, and leads to the formulation of the original and unique bipolar theory of life that represents a physical line of ascent from atom to man.

According to the theory, living matter is operated by electrical energy, and the author attempts to show that the materials of which animals are constructed are specifically adapted to electrical processes, that unit cells which drive the organism not only are adapted to fabricate, to store and to discharge electricity, but that protoplasm itself has these powers, that the organism as a whole is a bipolar electric mechanism bearing the pattern of the unit cells, and that the unit cells are constructed on the pattern of the atom, and, finally, that the normal and pathologic phenomena of man and animals can be interpreted in simple electrical terms.

In the proof of these ideas the author cites freely from the literature and more freely from his own experiments, some of which are not clear as to purpose, while others are based on a misinterpretation of fundamental physiologic facts. The experimental data, moreover, does not always bear on the points in question, and unwarranted conclusions are readily drawn. For example, in the attempt to substantiate the theory it is shown by experiment that the mammal is a bipolar mechanism, the positive pole of which is the brain while the negative pole, or "ground," is the liver. Thus, decerebration causes death simply by removing the positive pole of the battery, while liver ablation or disease that renders that organ nonfunctional removes the ground and produces death by making the circuit incomplete.

The theory embodies sound physiologic and chemical facts which are given electrical interpretations unreservedly and at times in neglect of other and better explanations of facts. The idea that all pathologic phenomena, including cancer, endocrine activity, reproduction and sex, etc., are the result of variations in electrical conductivity is unwarranted both from the evidence produced and from the known facts.

The material is presented in a pleasing manner, the book is well arranged and clearly expressed. It is interesting and original, but is of doubtful scientific value.

LES DIFFÉRENTES FORMES DE L'ARSENICISME Par KARL PETREN Cloth Price, \$10 Paris Masson et Cie

This volume is the French translation of the report of a commission of the Swedish government which investigated the subject of arsenicism exhaustively. In this edition the full case reports are omitted and only a few illustrative cases included. In its earlier stages this commission had the advantage of the services of Bang, and later of Ramberg and Wirgin, who elaborated microchemical methods by which infinitesimal amounts of arsenic could be accurately tested. Quantities as small as 0.0002 mg in 10 cc of blood can be recognized by this technic, which is based on the electrolytic reduction of arsenic at a mercury cathode.

In the first place, it was noted in an extensive analysis of foods that the fish from some regions of the Baltic as well as certain inland lakes contained appreciable amounts of arsenic, and that after ingestion of a single large meal of these fish the urine might contain as much as 1 mg of arsenic. Whatever the physiologic effects of such a phenomenon, it is doubtful whether it is the cause of any real arsenical poisoning, although it may be the culminating factor in certain cases in which the body is already saturated almost to the point of toxemia.

After fish is eaten, the arsenic in the blood may rise to the level of 0.0004 mg in 10 cc of blood. Vigorous medication with a solution of potassium arsenite (Fowler's solution) raises the blood arsenic to 0.0012-0.0014 mg in 10 cc, and a course of injections of arsphenamine may send these figures up to as high as 0.006 in 10 cc. However, such degrees of intoxication do not cause symptoms unless continued for a long period. Unfortunately, the true clinical cases of arsenicism were not submitted to blood tests, but in every case the exposure was at least six months, and more often it was a year. Reference is made to an epidemic of arsenicism that was caused by the prolonged ingestion in moderate amounts of beer that contained 4 mg of arsenic per liter.

Probably most of the cases investigated by the commission resulted from arsenic in the wall-paper or paint on household goods. The arsenic in the wall-paper in these reports varied from 4 to 35 mg in 200 sq cm.

The clinical picture of this condition is quite constant. Headache, fatigue, falling hair and gastro-intestinal disturbances initiate the disease. As these become more severe, insomnia and vertigo come on. The mouth and gums become sore. Conjunctivitis of a mild type is frequent. Loss of appetite, nausea and, in many cases, even vomiting appear. The polyneuritis of arsenicism may be severe. Areas of anesthesia, paresthesia and motor paralyses, especially in the extremities, are common features in the severe cases.

DIE HYPERTONIEKRANKHEITEN. VON DR. ESKIL KÄLIN, Direktor des Militärkrankenhauses in Eksjö, Sweden. Paper Price, 8.40 marks. Pp 168, with 22 illustrations. Berlin: Julius Springer, 1926.

The reviewer's task is not easy. This book contains a wealth of material on the newer aspects of hypertension, which if dug out from the unnecessary verbiage would form a fundamentally sound statement of facts and a stimulating array of theory. But it is extremely difficult to dig all this out.

The conception of a fundamental difference between essential hypertension and the hypertension of acute glomerulonephritis is well presented and discussed. Essential hypertension is the expression of an unknown result acting on the vegetative nervous system of certain persons of a peculiar constitutional make-up. There is in this disease no disturbance of the capillaries. The hypertension of glomerulonephritis is the result of injury to the capillary system. In neither instance need the kidney be primarily involved.

Most of the book is devoted to a discussion of the evidence leading to these conclusions. All interested in this vital problem should read the book.

BLOOD CHEMISTRY. COLORIMETRIC METHODS. By W. J. STONE. Ed. 2. Pp 129. New York: Paul B. Hoeber.

The author limits the contents of this book to the determination of certain chemical constituents of the blood and urine which have some clinical significance, particularly in metabolic disturbances. Colorimetric methods for determining blood urea, nonprotein nitrogen, uric acid, creatinine, chlorides, sugar and cholesterol are described. A modification of Folin's method for estimating the total nitrogen of urine is added. The titratable acidity of the urine, a procedure of doubtful clinical importance, is also mentioned. The brief comments on the significance of the variations of the important chemical constituents of the blood, as well as the suggestions on the dietary management of nephritis and diabetes, are an added feature which many larger books on blood chemistry lack. The methods selected are reliable, are clearly stated, and require relatively small amounts of blood, and can be readily performed in a small laboratory. This volume should be a useful practical manual not only for practitioners, for whom it is intended, but also for workers in small clinical or hospital laboratories.

INDEX TO VOLUME 38

	PAGE		PAGE
Achlorhydria See Stomach, acidity		Bloomfield, A. L.—Continued	
Achylia Gastrica, pernicious anemia and combined cord degeneration and their relationship	292	Effect of atropine on gastric function in man, quantitative study	303
Acids, organic, formation of, and retention of chlorides in lobar pneumonia	489	Method for continuous quantitative estimation of gastric secretion and discharge in man, (correction)	141
Ackman, F. D. Combining power of proteins with rose bengal, application as quantitative test on spinal fluid	527	Bogen, L. Arachnidism, spider poisoning	623
Aldrich, M. Urea retention, simple method for its estimation by mercury combining power of blood	474	Boles, R. S. Nontraumatic left diaphragmatic hernia, clinical and roentgenologic studies in 15 cases	633
Alvarez, W. C. Hypertension and constipation	158	Bone, defective development in, renal dwarfism, report of case	612
Anaphylaxis, local, experimental production of gastric ulcer by	237	long, growth of, in childhood, with special reference to certain bony striations of metaphysis and to role of vitamins	785
Andrews, E. Water metabolism, sugar metabolism in dehydration	136	BOOK REVIEWS	
Anemia pernicious	169	A Bipolar Theory of Living Processes, G. W. Calk	832
pernicious, achylia gastrica and combined cord degeneration and their relationship	292	Archives of Andrew Todd McClintock Memorial Foundation for the Study of Diseases of Alimentary Canal, Pleomorphism in Bacterial Protoplasm, Study in Psittacosis, A. T. McClintock	143
splenic (Banti's disease)	171	Art of Medical Treatment, F. W. Palfrey	143
Aneurysm mycotic	226	Blood Chemistry Colorimetric Methods, W. J. Stone	834
mycotic, of aorta	367	Classification of Strains Belonging to Typhoid Paratyphoid Group of Bacteria Together with Demonstration of Differences in Avidity, A. Hecht-Johnsen	412
Aorta, mycotic aneurysm of	367	Development of Our Knowledge of Tuberculosis, L. F. Fliet	278
stenosis of isthmus (coarctation) of, its diagnosis during life 69, (correction)	409	Die Hypertoniekrankheiten, E. Kylin	834
Arachnidism See Spider poisoning		Diseases of the Heart, H. Vaquez	410
Arrhythmia cordis epigastric pulsation diagnosis of, through epigastriogram	360	Facts on the Heart, R. C. Cabot	551
Aspiration, rationale of therapeutic puncture in pericardial effusions, experimental study	206	Ibuprofen y Flutter Auricular, M. Velh Gonzalez	552
Atropine, effect of, on gastric function in man, quantitative study	303	Food for Diabetic, M. P. Hussleson	412
Auricular fibrillation with regular ventricular rhythm and rate over 60	116	Gastric Function in Health and Disease, I. A. Ryle	276
		Immunochemical Studies, C. H. Brown	276
Baldrige, C. W. Glandular fever, infectious Mononucleosis	413	Investigations into Morphology of Ray Fungi, J. Orskov	412
Bazin, L. V. Output of heart per beat in hyperthyroidism	566	La Arteritis Pulmonar, Cardiacos Negros, F. C. Arrillaga	278
Bellinger, M. Chemical changes in blood during fasting in human subject	553	Les Différentes Formes de l'Arsenisme, K. Petren	833
Benedict, F. G. Insensible perspiration, its relation to human physiology and pathology	1	Les Maladies Des Glandes Endocrines, K. H. Krabbe	684
Beriberi, basal metabolism in	770	Le Terrain Heredo Syphilitique, V. Hutinel	683
Berk, A. Sodoku in treatment of general paralysis, preliminary report	391	Manual of Clinical Laboratory Methods, C. L. Cummer	277
Bile, regulation of flow of, and pancreatic juice into duodenum	647	Medical Diagnosis, J. M. Anders and L. Napoleon	411
Biliary Tract, chronic disease of, diagnostic criteria	708	Nephritis, H. Elwyn	277
Blister, capillary permeability and inflammatory index of skin in normal person as determined by	663	Nervous and Mental Disorders from Birth Through Adolescence, B. Sachs and L. Hausman	832
Blood, changes in chemical and physical characteristics of, following administration of parathyroid hormone, with special reference to clotting of blood	502	Physical Diagnosis of Diseases of the Chest, Pratt & Bushnell	411
chemical changes in, during fasting in human subject	553	Physiotherapy, H. E. Stewart	142
pressure, high, and constipation	158	Psychoneurolysis and Beyond Psychoanalysis, L. L. Landis	277
pressure, high, basal metabolic rate in cases of chronic cardiac disease and	385	Rheumatic Heart Disease, C. F. Coombs	551
pressure, systolic and diastolic, relative importance of, in maintaining coronary circulation	109	Scoliosis, S. Kleinberg	276
quantities of serum albumin, globulin and fibrinogen in blood plasma in acute and chronic nephropathies	510	Studies of Gonococcus Types and Gonococcus Immune Serums, E. Vollmond	412
tests, and in diagnosis of typhoid fever, new laboratory method	544	Studies on Papillae Vallate of Man, A. Jurisch	412
urea retention, simple method for its estimation by mercury combining power of blood	474	Synopsis of Medicine, H. L. Tidy	142
Bloomfield, A. L. Clinical physiology of stomach, simultaneous quantitative observations on gastric secretory volume, acidity and motility	145	The International Medical Annual, A Year Book of Treatment and Practitioner's Index Forty Fourth Year, 1926	684
		The Principles and Practice of Endocrine Medicine, W. N. Berkeley	682

	PAGE		PAGE
Brown, G E Spectrophotometric analysis of color of skin, and observations by this method in normal and pathologic subjects	816	Fasting, chemical changes in blood during, in human subject	553
Treatment of polycythemia vera (erythremia) with phenylhydrazine	321	Feinblatt, H M Carcinoma of cortex of suprarenal gland with virilism, case with necropsy	469
Cantarow, A Changes in chemical and physical characteristics of blood following administration of parathyroid hormone, with special reference to clotting of blood	502	Fishberg, A M Unitary nature of impairment of renal function	259
Modification of urea concentration test	581	Fleisher, M S Relation of monilia to infections of upper air passages	217
Capillary permeability and inflammatory index of skin in normal person as determined by blister	663	Fuku, N Epigastric pulsation, diagnosis of arrhythmia cordis through epigastric triogram	360
permeability, relation of menstruation to autonomic tonus of skin vessels and	730	Galambos, A Direct examination of gastric juice, new functional test	654
Carcinoma of cortex of suprarenal gland with virilism, case with necropsy	469	Gallbladder, chronic biliary tract disease, diagnostic criteria	708
primary, of thymus	807	Giffin, H Z Treatment of polycythemia vera (erythremia) with phenylhydrazine	321
Caven, W R Changes in chemical and physical characteristics of blood following administration of parathyroid hormone, with special reference to clotting of blood	502	Glandular fever, infectious mononucleosis	413
Cerebrospinal Fluid, tests, combining power of proteins with rose bengal, application as quantitative test on spinal fluid	527	Glycosuria, benign, occurrence of, in diabetic families	279
Chloride, retention, formation of organic acids and, in lobar pneumonia	489	Gold, H Persistent premature contractions, clinical study	186
retention, unitary nature of impairment of renal function	268	Gordon, B Changes in chemical and physical characteristics of blood following administration of parathyroid hormone, with special reference to clotting of blood	502
Clay, C L Sodoku in treatment of general paralysis, preliminary report	391	Graber, V C Coronary thrombosis with congenital absence of left coronary artery	222
Cocaine, poisoning, acute, its treatment in monkey (Macacus rhesus)	405	Relative importance of systolic and diastolic blood pressure in maintaining coronary circulation	109
Collins, K H Acute cocaine poisoning and its treatment in monkey (Macacus rhesus)	405	Greene, C H Diseases of liver, comparative study of tests for hepatic function in certain diseases of hematopoietic system	167
Conner, H M Diseases of liver, comparative study of tests for hepatic function in certain diseases of hematopoietic system	167	Grinker, R R Pernicious anemia, achylia gastrica and combined cord degeneration and their relationship	292
Constipation and hypertension	158	Hansmann, G H Glandular fever, infectious mononucleosis	413
Contractions, persistent premature, clinical study	186	Mycotic aneurysm of aorta	367
Copher, G H Regulation of flow of bile and pancreatic juice into duodenum	647	Harris, H A Growth of long bones in childhood, with special reference to certain bony striations of metaphysis and to role of vitamins	785
Coronary circulation, relative importance of systolic and diastolic blood pressure in maintaining	109	Heart, auricular fibrillation with regular ventricular rhythm and rate over 60	116
thrombosis, with congenital absence of left coronary artery	222	cardiac capacity determined by standardized effort, preliminary report	761
Diabetes Mellitus, benign glycosuria in diabetic families	279	diseases, chronic, basal metabolic rate in, and in hypertension	385
hyperthyroidism, myxedema and	736	output of, per beat in hyperthyroidism	566
insulin by mouth	779	sounds, analysis of	685
role of insulin in protein metabolism	96	Hematopoietic System, diseases of liver, comparative study of tests for hepatic function in certain diseases of hematopoietic system	167
Dodge, H F Analysis of heart sounds	685	Hench, P S Urea retention, simple method for its estimation by mercury combining power of blood	474
Duodenum, regulation of flow of bile and pancreatic juice into	647	Henderson, W S Chronic biliary tract disease, diagnostic criteria	708
ulcer See Peptic Ulcer		Heredity, occurrence of benign glycosuria in diabetic families	279
Dwarfism, renal, report of case	612	Hernia, diaphragmatic, nontraumatic left, clinical and roentgenologic studies in 15 cases	633
Dynamometer, cardiac capacity determined by standardized effort, preliminary report	761	Hines, L E Peristalsis in loop of small intestine, direct study	536
Edema, correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema	57	Holst, J E Occurrence of benign glycosuria in diabetic families	279
pharmacology and therapeutics of novasurol	374	Holten, C Formation of organic acids and retention of chlorides in lobar pneumonia	489
Elastometer findings, correlation of disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema	57	Hypertension See Blood pressure, high	
Elwyn, H Pathogenesis of lipid nephrosis	346	Hyperthyroidism, external factors causing variable results in Kottmann reaction	129
Epigastric pulsation, diagnosis of arrhythmia cordis through epigastric triogram	360	myxedema, diabetes and	736
Erysipelas, roentgen ray therapy in	573	output of heart per beat in	566
Erythremia See Polycythemia		Hypnotics in acute cocaine poisoning	405
Ets, H N Rationale of therapeutic puncture in pericardial effusions	206	Insulin, role of, in protein metabolism	96
Fabr, G Quantities of serum albumin globulin and fibrinogen in blood plasma in acute and chronic nephropathies	510	use of, by mouth	779

INDEX TO VOLUME 38

	PAGE		PAGE
Intestines, motility, peristalsis in loop of small intestine, direct study	536	Mental Disease, external factors causing variable results in Kottmann reaction	129
Ito, A C Gastric ulcer, experimental production of gastric ulcer by local anaphylaxis	237	Mercury, urea retention, simple method for its estimation by mercury combining power of blood	474
Jancy, N W Role of insulin in protein metabolism	96	Metabolism See also Protein metabolism, Sugar metabolism, Water metabolism	
Japanese, basal metabolism of	590	basal, in beriberi	770
Jaundice hemolytic	168	basal metabolic rate in cases of chronic cardiac disease and in cases of hypertension	385
Jones, H W Modification of urea concentration test	581	basal, of Japanese	590
Kameda, T Basal metabolism of Japanese	590	chemical changes in blood during fasting in human subject	553
Kasamun, J External factors causing variable results in Kottmann reaction	129	insensible perspiration, its relation to human physiology and pathology	1
Kawahara, S Rate of urea excretion as test of renal function by means of modification of McLern's index	36	Metaphysis, growth of long bones in child hood, with special reference to certain bony striations of metaphysis and to role of vitamins	785
Keefer, C S Clinical physiology of stomach, simultaneous quantitative observations on gastric secretory volume, acidity and motility	145	Miller, G H Relative importance of systolic and diastolic blood pressure in maintaining coronary circulation	109
Effect of atropine on gastric function in man, quantitative study	303	Miller, H R Use of insulin by mouth	779
Kidney diseases, lipid nephrosis	449	Milles, G Relation of menstruation to permeability of skin capillaries and autonomic tonus of skin vessels	730
diseases, pathogenesis of lipid nephrosis	346	Mills, C A Aid in diagnosis of typhoid fever, new laboratory method	544
diseases quantities of serum albumin, globulin and fibrinogen in blood plasma in acute and chronic nephropathies	510	Monilia, relation of, to infections of upper air passages	217
function, unitary nature of impairment of	259	Mononucleosis See under Glandular Fever	
function test, modification of urea concentration test	581	Murphy, F D Lipoid nephrosis	449
function test, rate of urea excretion as test of renal function by means of modification of McLern's index	36	Mycotic aneurysms, 2 cases	226
function test, urea retention, simple method for its estimation by mercury combining power of blood	474	aneurysm of aorta	367
insufficiency, renal dwarfism, report of case	612	Myxedema, hyperthyroidism, diabetes and	736
pharmacology and therapeutics of novasurol	374	Nitrogen retention of blood in edema, correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and	57
King, J T, Jr Stenosis of isthmus (correction) of aorta and its diagnosis during life, 69, (correction)	409	Novasurol, pharmacology and therapeutics of	374
Kitzmiller, K V Aid in diagnosis of typhoid fever, new laboratory method	544	O'Connor, M Chemical changes in blood during fasting in human subject	553
Knapp, E External factors causing variable results in Kottmann reaction	129	Okada, S Basal metabolism in beriberi	770
Kodama, S Regulation of flow of bile and pancreatic juice into duodenum	647	Basal metabolism of Japanese	590
Kothis, A J Relation of monilia to infections of upper air passages	217	Otto, H L Persistent premature contractions, clinical study	186
Kottmann Reaction See Thyroid function test		Pain, mechanism of, in gastric and duodenal ulcers, achlorhydria	603
Kunde, M M Edema, correlation of elastometer findings, disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema	57	mechanism of, in gastric and duodenal ulcer, production of pain by means of chemical irritants	694
Lathrop, F W Renal dwarfism	612	Palmer, W L Mechanism of pain in gastric and duodenal ulcers, achlorhydria	603
Lers, R D Mycotic aneurysms	226	Mechanism of pain in gastric and duodenal ulcer, production of pain by means of chemical irritants	694
Lemann, I I Primary carcinoma of thyroid, report of case	807	Pancoast, H K Nontraumatic left diaphragmatic hernia, clinical and roentgenologic studies in 15 cases	633
Lennox, W G Chemical changes in blood during fasting in human subject	553	Pancreatic juice, regulation of flow of bile and, into duodenum	647
Leukemia	176	Paralysis, general, sodoku in treatment of	391
Levy, R L Auricular fibrillation with regular ventricular rhythm and rate over 60	116	Parathyroid hormone, changes in chemical and physical characteristics of blood following administration of, with special reference to clotting of blood	502
Lipoid nephrosis	449	Peptic Ulcer, experimental production of gastric ulcer by local anaphylaxis	237
nephrosis, pathogenesis of	346	gastric and duodenal ulcer, frequency, number, size, shape, location, color sex and age in 7,700 necropsy records at Bellevue Hospital, New York	41
Liver diseases, comparative study of tests for hepatic function in certain diseases of hematopoietic system	167	mechanism of pain in gastric and duodenal ulcers, achlorhydria	603
McCalla, R L Hypertension and constipation statistical inquiry	158	mechanism of pain in gastric and duodenal ulcer, production of pain by means of chemical irritants	694
McLern's Index See Kidney, function test		Pericardial effusions, rationale of therapeutic puncture in, experimental study	206
Mateer, J G Chronic biliary tract disease, diagnostic criteria	708	Peristalsis See Intestines, motility	
Mead, H C A Peristalsis in loop of small intestine, direct study	536	Perspiration, insensible, its relation to human physiology and pathology	1
Menstruation, relation of, to permeability of skin capillaries and autonomic tonus of skin vessels	730	Petersen, W F Capillary permeability and inflammatory index of skin in normal person as determined by blister	663

	PAGE		PAGE
Petersen, W F—Continued		Splcnomegaly of Grucher type	173
Relation of menstruation to permeability of skin capillaries and autonomic tonus of skin vessels	730	Stomach, acidity, mechanism of pain in gastric and duodenal ulcers, achlorhydria	603
Phenylhydrazine, treatment of polycythemia vera (erythremia) with	321	direct examination of gastric juice, new functional test	654
Platou, E S Roentgen ray therapy in erysipelas	573	effect of atropine on gastric function in man, quantitative study	303
Pneumonia, formation of organic acids and retention of chlorides in	489	gastric secretion and discharge, method for continuous quantitative estimation of, (correction)	141
Polycythemia vera (erythremia)	175	simultaneous quantitative observations on gastric secretory volume, acidity and motility	145
vera (erythremia), treatment of, with phenylhydrazine	321	ulcer See Peptic Ulcer	
Protein, combining power of, with rose bengal, application as quantitative test on spinal fluid	527	Sturtevant, M Gastric and duodenal ulcer, frequency, number, size, shape, location, color, sex and age in 7,700 necropsy records at Bellevue Hospital, New York	41
metabolism, role of insulin in	96	Sugar metabolism in dehydration	136
Rabinowitch, I M Output of heart per beat in hyperthyroidism	566	Suprarenals, carcinoma of cortex of, with virilism, case with necropsy	469
Respiratory Tract, infections, relation of monilia to	217	Swanson, W W Quantities of serum albumin, globulin and fibrinogen in blood plasma in acute and chronic nephropathies	510
Rigler, L Roentgen ray therapy in erysipelas	573	Tatum, A L Acute cocaine poisoning and its treatment in monkey (<i>Macacus rhesus</i>)	405
Roentgen ray therapy in erysipelas	573	Thatcher, H S Mycotic aneurysms	226
Rohner, F J Glandular fever, infectious mononucleosis	413	Theiler, M Sodoku in treatment of general paralysis, preliminary report	391
Root, H F Insensible perspiration, its relation to human physiology and pathology	1	Thrombosis, coronary, with congenital absence of left coronary artery	222
Rose Bengal Test See under Proteins		Thymus, primary carcinoma of, report of case	807
Rosenthal, S M Combining power of proteins with rose bengal, application as quantitative test on spinal fluid	527	Thyroid, function test, external factors causing variable results in Kottmann reaction	129
Sakurai, E Basal metabolism in beriberi	770	Typhoid diagnosis of, new laboratory method	544
Basal metabolism of Japanese	590	Urea concentration test, modification of excretion, rate of, as test of renal function by means of modification of McLenn's index	36
Salt solution, edema, correlation of elastometer findings, disappearance time for intradermally injected salt solution		retention, simple method for its estimation by mercury combining power of blood	474
urinalysis and nitrogen retention of blood in edema	57	Uremia, unitary nature of impairment of renal function	259
Serby, A M Pharmacology and therapeutics of novasurol	374	Urine, analysis, edema, correlation of elastometer findings disappearance time for intradermally injected salt solution, urinalysis and nitrogen retention of blood in edema	57
Shapiro, I Role of insulin in protein metabolism	96	in impaired renal function	266
Shapiro, L L Gastric and duodenal ulcer, frequency, number, size, shape, location, color, sex and age in 7,700 necropsy records at Bellevue Hospital, New York	41	Virilism, carcinoma of cortex of suprarenal gland with, case with necropsy	469
Shapiro, P F Gastric ulcer, experimental production of gastric ulcer by local anaphylaxis	237	Vitamins, growth of long bones in childhood, with special reference to certain bony striations of metaphysis and to role of vitamins	785
Shapiro, S Basal metabolic rate in cases of chronic cardiac disease and in cases of hypertension	385	Wachowiak, M Relation of monilia to infections of upper air passages	217
Sheard, C Spectrophotometric analysis of color of skin, and observations by this method in normal and pathologic subjects	816	Warfield, L M Lipoid nephrosis	449
Skin, capillary permeability and inflammatory index of, in normal person as determined by blister	663	Water metabolism, sugar metabolism in dehydration	136
capillaries, relation of menstruation to permeability of, and autonomic tonus of skin vessels	730	Wilder, R M Hyperthyroidism, myxedema and diabetes	736
spectrophotometric analysis of color of, and observations by this method in normal and pathologic subjects	816	Williams, H B Analysis of heart sounds	685
Smith, F M Coronary thrombosis with congenital absence of left coronary artery	222	Williamson, C S Rationale of therapeutic puncture in pericardial effusions, experimental study	206
Mycotic aneurysm of aorta	367	Willis, D A Capillary permeability and inflammatory index of skin in normal person as determined by blister	663
Relative importance of systolic and diastolic blood pressure in maintaining coronary circulation	109	Wolfe, J B Cardiac capacity determined by standardized effort, preliminary report	761
Smith, J Primary carcinoma of thymus, report of case	807	Zimmermann, A Hypertension and constipation, statistical inquiry	158
Sodoku in treatment of general paralysis	391		
Solomon, H C Sodoku in treatment of general paralysis, preliminary report	391		
Spectrophotometric analysis of color of skin, and observations by this method in normal and pathologic subjects	816		
Spider poisoning, arachnidism	623		
Spinal Cord, degeneration, relationship of pernicious anemia, achylia gastrica and	292		

